

SYNTHETIC AND STEREOCHEMICAL INVESTIGATIONS IN
CARBOHYDRATE CHEMISTRY

by

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ABSTRACT OF THESIS

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Title of Thesis Synthetic and Stereochemical Investigations in
Carbohydrate Chemistry.

The contents of this thesis are concerned for the most part with studies on the methoxymercuration of glycals. This reaction was studied to elucidate the stereochemistry of addition and to discover the suitability, or otherwise, of sugar methoxymercurials as starting materials for the preparation of 2-substituted glycosides.

The salient features of the oxymercuration reaction and the more important properties of the adducts are discussed in the Introduction, with particular attention being paid to the mechanism and stereochemistry of the reaction.

The stereochemistry of addition of OMe and HgX groups to several glycals was examined to ascertain whether groups not directly attached to the double bond affected the direction of initial attack of the mercury group to the glycal double bond. Other factors which may determine the stereochemistry of addition were also considered. The structures of the mercurials prepared have been established by chemical, X-ray and N.M.R. methods. This work is discussed in Part I.

In Part II is described the attempted introduction of acetoxyl and nitroso groups into the pyranose ring by the replacement of the mercury in sugar methoxymercurials by treatment with lead tetraacetate and nitrosyl chloride reagents respectively. It was found that elimination to the glycal appeared to occur more readily than the replacement of the mercury in these reactions and this result indicates the unsuitability of sugar mercurials as starting materials for the preparation of 2-substituted glycosides. This work led to a study of the interesting reactions of D-glucal triacetate with lead tetraacetate in various solvents.

In Part III, the slow reactions occurring on the addition of

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a glycal to a sugar mercuriacetate were examined and partially elucidated. It was shown that one of the reactions involved a trans-mercuration equilibrium, in which the mercury group was transferred from one sugar residue to the other. The reaction of D-glucal triacetate with phenyl mercuriacetate in methanol was studied in an attempt to understand the modification of the glycal by the mercuriacetate group which also occurred under these conditions. In connection with this work, it was found that sodium acetate in methanol caused the deacetylation of acetylated carbohydrates and the kinetics of this reaction were examined.

Part IV concerns the application of the Conformational Dissymmetry Rule to the calculation of the optical rotations of sugar mercurials, and of methylated sugars and related compounds. Preliminary experiments on the application of circular dichroism and optical rotatory dispersion in carbohydrate chemistry are mentioned also.

TO
MY WIFE
AND
MY PARENTS

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PREFACE

The contents of this thesis are concerned for the most part with studies on the oxymercuration of glycols.

The Introduction gives a brief account of the addition of OR and HgX groups to olefins, with particular reference to the more recent work on the mechanism and stereochemistry of the reaction.

Oxymercuration adducts of several glycols were prepared in order to elucidate the stereochemistry of the addition. The structures of the mercurials prepared have been established by chemical, X-ray and N.M.R. methods. This work is reported in Part I.

The attempted replacement of mercury in carbohydrate mercurials by treatment with reagents such as lead tetraacetate and nitrosyl chloride is discussed in Part II. This work led to a study of the interesting reactions of D-glucal triacetate with lead tetraacetate in various solvents.

In Part III the slow side reactions encountered in a competition experiment between D-glucal and D-galactal triacetates for methanolic mercuric acetate are discussed. In connection with this it was found that sodium acetate in methanol caused the deacetylation of acetylated carbohydrates and the kinetics of this reaction are examined.

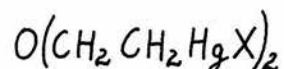
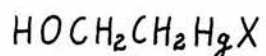
Part IV concerns the application of the Conformational Dissymmetry Rule¹ to the optical rotations of sugar mercurials,

and of methylated sugars and related compounds. Preliminary experiments on the application of circular dichroism and optical rotatory dispersion in carbohydrate chemistry are mentioned.

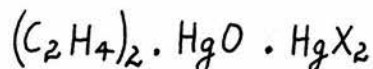
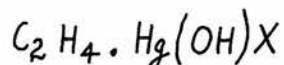
INTRODUCTION

It is over sixty years since the reaction of alkenes with aqueous mercuric salts was first reported by Hofmann and Sand.² Since that time a great deal of controversy has centred around these alkene-mercury compounds particularly with reference to their structures, stereochemistry and mechanism of formation.

Further work by Hofmann and Sand in the period 1900 - 1908 led them to believe that the reaction involved the addition of basic mercuric salts to the double bond to give two types of products.



The most characteristic reaction of the olefin-mercury addition compounds is the ease with which they regenerate the olefin in the presence of halogen acids. This instability, which is in marked contrast to the stability of alkyl mercury halides with acids, led Manchot and Klug^{3,4} to propose that true addition had not taken place and that the products were simply molecular complexes of the type,

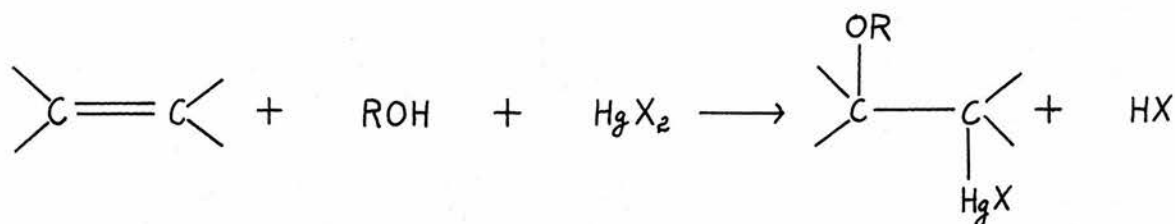


which are analogous to known coordination complexes of olefins with such metals as platinum, copper and silver.

That the alkene-mercury products were true addition compounds and not coordination complexes was proved by the reaction

of mercuric acetate with o-allyl phenol. The adduct obtained gave 2-iodomethyl-2,3-dihydrobenzofuran on replacement of the mercury group by iodine.^{5,6} Further proof was furnished by Sandborn and Marvel⁷ who observed that in the oxymercuration of optically active cinnamic esters two new asymmetric centres were produced.

The general equation for the oxymercuration reaction is shown below:



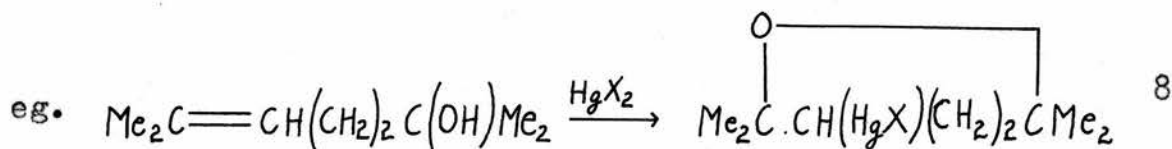
where R=H, Me, COCH₃ etc.,

and X=OCOCH₃, NO₃, Cl etc.

Oxymercuration can be easily carried out by allowing the alkene to react with the mercuric salt, usually mercuric acetate, in a hydroxylic medium such as water or methanol. Mercuric acetate is favoured in mercurations because it has the advantage that the acetic acid produced is too weak an acid to make the reverse reaction significant. The acetate group in the adduct is ionised and can be easily replaced by other ions by double decomposition with inorganic salts. Mercurials are usually converted to the mercurichlorides as these are the least soluble and the most stable.

When the olefin contains a hydroxyl group which can act as

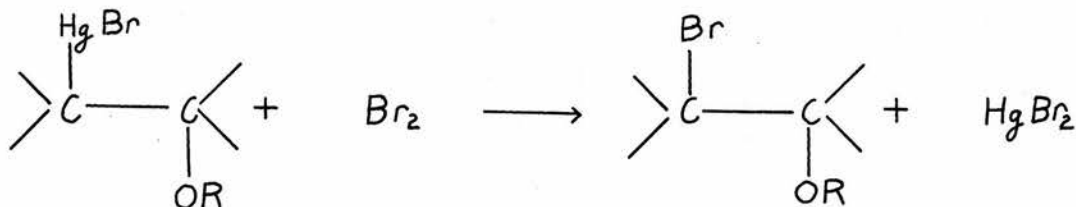
an anionic source, then addition of mercuric salt to the neat olefin, or to the olefin dissolved in an inert medium, results in exclusive formation of a mercurial having an internal ether link.



Oxymercuration involves specificity of addition because if the alkene is capable of geometrical isomerism, then each geometric isomer will react to give a characteristic diastereoisomer uncontaminated with the other.

Oxymercurials are usually crystalline compounds which dissolve completely in alkali forming the mercurihydroxide; they are precipitated out again unchanged by careful neutralisation with the appropriate acid.

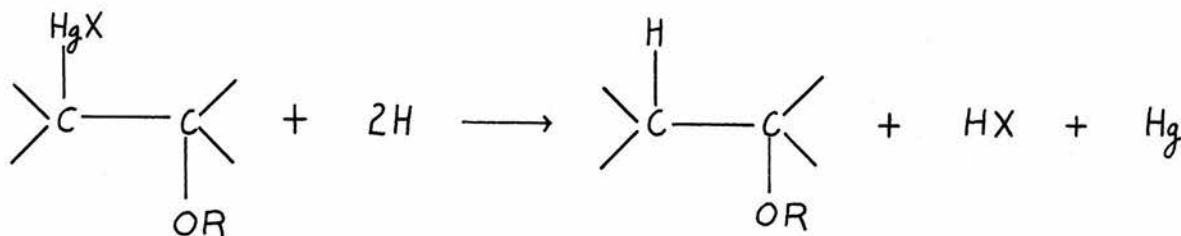
The mercury group can be conveniently split off by treatment with iodine or bromine to give the corresponding halogeno compound. This was the first method evolved for finding the position of the mercury atom in the adduct.



The replacement of mercury by bromine, which has been claimed to proceed with retention of configuration using bromine in a polar solvent,⁹ has been used to ascertain the configuration

of the mercury in methoxymercurials from D-glucal and its triacetate.¹⁰ The unreliability of this method is discussed in Part I.

The reduction of a mercurial in alkali replaces the mercury atom by hydrogen according to the equation:



This method has been used to determine the configuration of the glycoside grouping in the methoxymercurials of various sugars, by identification of the known deoxy-glycoside produced on reduction.¹¹ (Part I)

Free Radical Isomerisation of Cycloolefin Mercurials.

The methoxymercuration of cyclohexene yields one mercurial only, which has been termed the α - or "labile" isomer by Romeyn and Wright.¹² Epimerization of the C—Hg bond in this compound to give the β - or "stable" isomer can be brought about by boiling in ethanol in the presence of small amounts of catalysts such as hydrazine hydrate, diphenyl mercury and benzoyl peroxide. This array of catalysts has in common the ability of converting RHgCl to R_2Hg by a free radical interchange. Acidification of the product decomposes the α -compound preferentially and thus the β -isomer is obtained.¹²

In the simple cycloolefins it has always been found that the β -isomer has a higher dipole moment and a greater

resistance to acid deoxymercuration than the α -isomer.¹³ However, the reverse is true for mercurials of strained olefins, eg. norbornene, the mercurial obtained by direct mercuration being the acid stable isomer and having the higher dipole. This observation led Wright et al¹⁴ to propose that the stereochemistry of addition of OR and HgX groups to strained cycloolefins is different to that for addition to unstrained olefins. The full significance of this observation is discussed later.

By means of an asymmetric synthesis using mercuric L-lactate and subsequent replacement with sodium chloride, a pure laevorotatory cyclohexyl α -methoxymercurichloride, $[\alpha]_D -40^\circ$ (EtOH), has been isolated.¹² Free radical isomerisation gave a dextrorotatory β -isomer, $[\alpha]_D +13^\circ$ (EtOH). An attempt¹⁵ has been made to assign configurations to these mercurials from their molecular rotations using the Conformational Dissymmetry Rule.¹ This attempt, along with a similar attempt to assign structures to the sugar methoxymercurials, is discussed in Part IV.

The chemical reactions of olefin-mercury adducts tell us little as to their mechanism of formation and stereochemistry. As these subjects have been topics of great disagreement over the years and have not been completely resolved to this day, they will be considered now.

Mechanism and Stereochemistry of Oxymercuration Addition.

(i) Measurement of Equilibrium.

As stated above olefin-mercury adducts are easily decomposed by acids to the alkene. This decomposition can sometimes be caused by the acid produced in mercuration such that an equilibrium is set up in the reaction.

The strength of the acid produced in mercuration has a considerable influence on the rate and completeness of the reaction. Thus, the methoxymercuration of cyclohexene with mercuric chloride proceeds extremely slowly with the formation of less than 3% mercurial. When mercuric acetate is used the reaction goes rapidly to completion and no reversal can be effected by treating the adduct with acetic acid. With mercuric trifluoroacetate, whose associated acid is intermediate in strength between hydrochloric and acetic acids, a measurable equilibrium, which can be approached from both directions, is set up when 65% adduct/35% mercuric salt are present.¹⁶

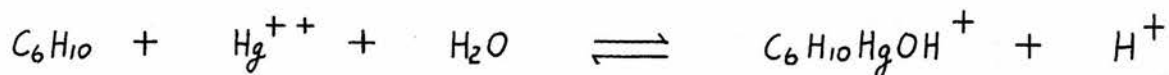
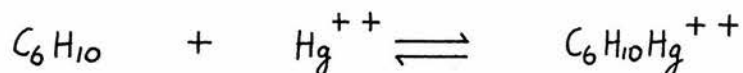
(ii) Rate of Reaction.

The rate of oxymercuration is particularly susceptible to catalysis. In general, electron donors such as nitriles and amines, which complex with mercuric salts, exert a strong retarding effect, while electron acceptors, such as boron trifluoride, have been found to accelerate the reaction. This catalysis does not affect all mercurations equally, being more pronounced in slow reactions.

In many studies on the kinetics of oxymercuration

cyclohexene has been used as the reacting olefin because it has the advantage that only one mercurial is formed.

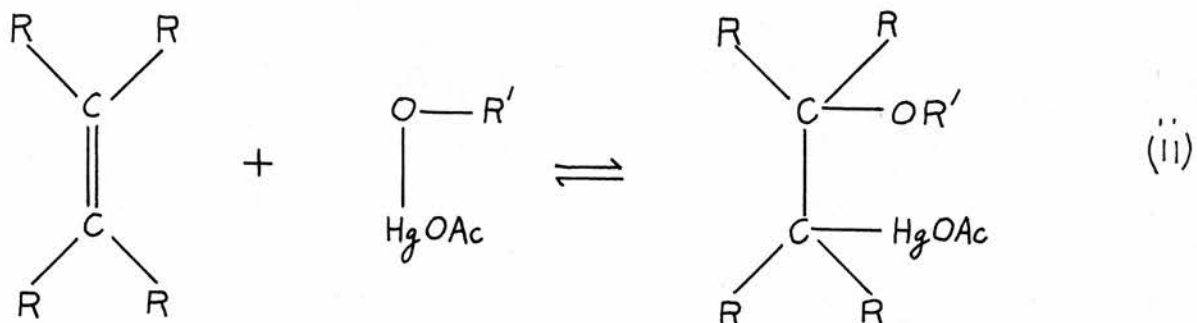
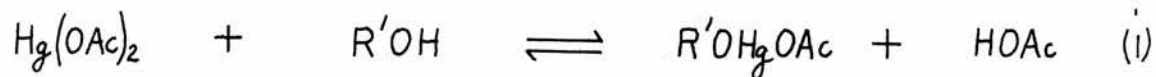
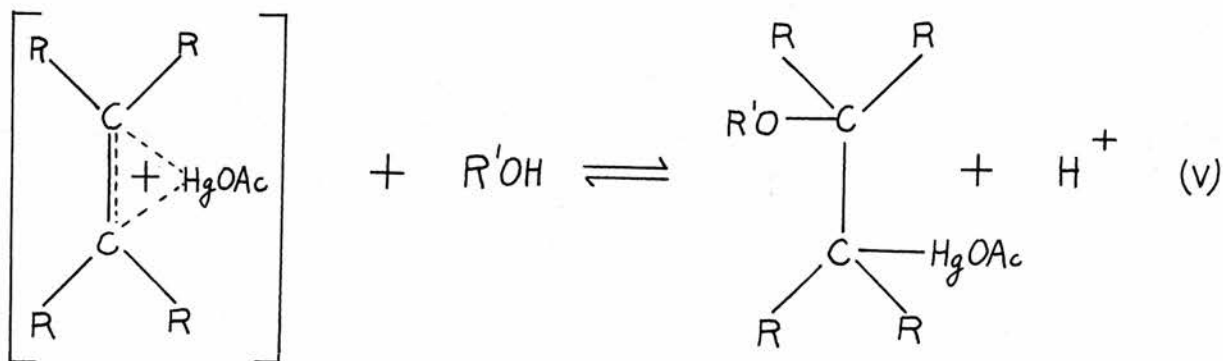
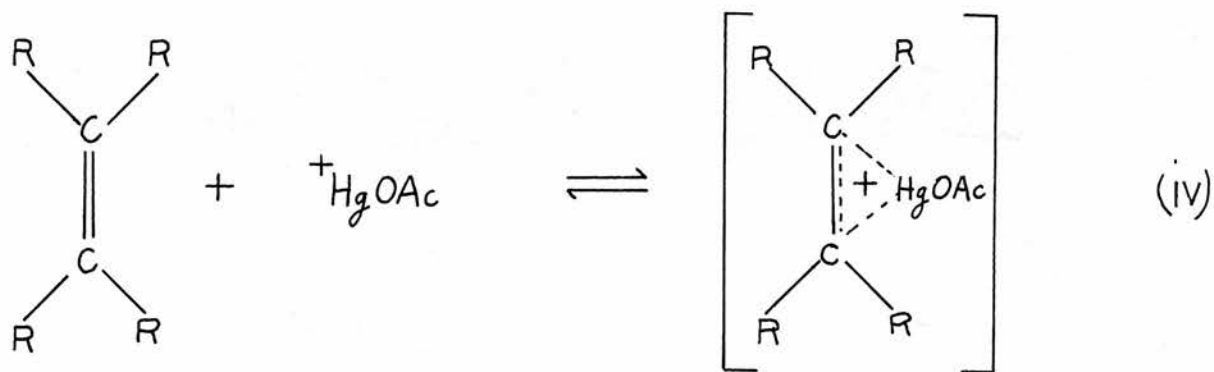
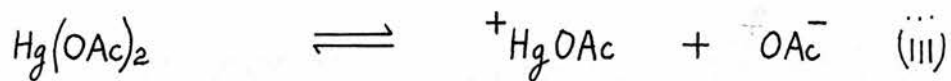
Lucas, Hepner and Winstein¹⁷ studied the kinetics of oxymercuration by determining the distribution of cyclohexene between carbon tetrachloride and an aqueous solution of mercuric nitrate, potassium nitrate and nitric acid at ionic strength, $\mu=1$. Their results suggested that two equilibria were rapidly established,



the latter being the more important. These workers considered that the oxymercuration of olefins proceeded through a mercurinium ion which was analogous to the bromonium intermediate proposed for bromine addition.¹⁸

Romeyn and Wright,¹² from studies on the reaction of cyclohexene with mercuric acetate in methanol, found that oxymercuration was first order with respect to olefin and to mercuric salt in excess hydroxylic solvent. These workers proposed that oxymercuration proceeded by a non-ionic mechanism involving the addition of oxymercuric salt, $ROHgOAc$, to the olefin.

The mechanism of the reaction will now be considered further.

Mechanism I.Mechanism II.

(iii) Mechanism and Stereochemistry.

Earlier workers in this field considered that oxymercuration involved addition of mercuric acetate to the olefin, followed by replacement of acetoxy by alkoxy by reaction with the solvent. Although it is known that mercuric acetate adds to olefins, the rate of formation of these adducts is too slow for them to be considered as intermediates in alkoxymercuration.¹⁹

Although peroxides catalyse oxymercuration, a free radical mechanism can be excluded because of the high degree of stereospecificity of addition.

Any mechanism with pretensions to completeness must explain in addition to the second order kinetics, the degree of specificity encountered. Two mechanisms merit consideration.

Mechanism I championed by Wright and his school^{19,20} involves the initial solvolysis of the mercuric salt by hydroxylic reagent to give the oxymercuric salt which then adds to the olefin. This non-ionic mechanism leads to cis addition.

Mercuric acetate, a salt of a weak acid and base, is known to solvolyse in hydroxylic media according to equation (i). It would be expected therefore that the addition of acetic acid to the mercuration mixture would reduce solvolysis and retard a non-ionic mechanism. On the other hand, if a mercurinium ion was involved acetic acid would be expected to accelerate the reaction by reducing solvolysis and increasing the ion population. Rodgman and Wright²⁰ found that acetic acid retards the oxymercuration of cyclohexene, the retardation

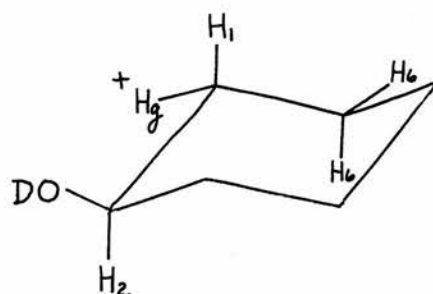
being proportional to the acid concentration. Sodium acetate was also found to exert a retarding influence but this was attributed to the formation of tetraacetoxymercurate ion, $\text{Hg}(\text{OAc})_4^{--}$, which could not participate in oxymercuration.

In recent studies by Mallik and Das²¹ on the methoxymercuration of acrylic esters, no acetic acid retardation was reported, on the contrary, a slight acceleration was observed. In addition, these workers propose that the retarding effect of sodium acetate is too large to be accounted for by complex ion formation. These observations are strong evidence for the existence of an ionic intermediate in oxymercuration.

The currently held view is that oxymercuration proceeds by Mechanism II proposed by Lucas et al.,¹⁷ involving a mercurinium ion intermediate and leading to trans addition of groups.

It is clear that the elucidation of the stereochemistry of the addition would provide a criterion for distinguishing between the two mechanisms. It was claimed from X-ray evidence that the methoxymercuration of cyclohexene had proceeded with trans addition of groups.²² Although Wright et al.²³ have since shown that this evidence is unreliable, other physical and chemical studies on the oxymercuration of unstrained cyclo and aliphatic olefins have provided convincing proof that trans addition has taken place.

Thus, the N.M.R. spectrum of the mercuration product of cyclohexene in D_2O gives the following coupling constants.²⁴



J_{16} ae 3.5 c.p.s.

J_{16} aa 10.0 c.p.s.

J_{12} aa 10.0 c.p.s.

The larger coupling constants are similar to those found by Lemieux et al for axial-axial (aa) proton coupling in six membered rings, the smaller value being reasonable for axial-equatorial (ae) coupling.^{25,26} The existence of two aa coupling constants for $H_{(1)}$ indicates that both H_g and OD are in equatorial positions, the configuration of the hydroxymercuration product is therefore trans.

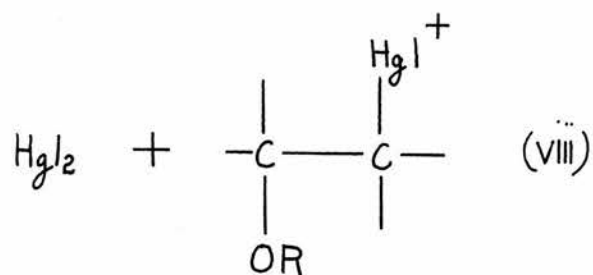
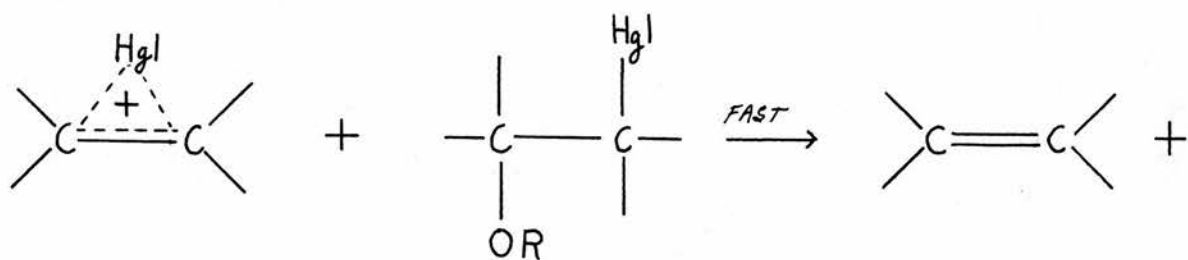
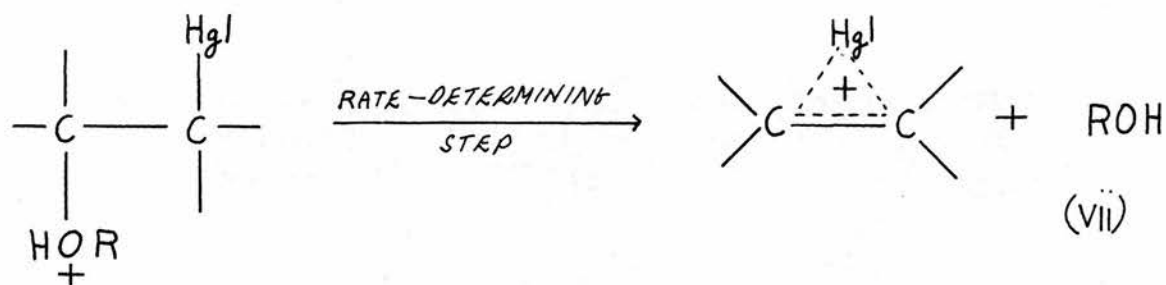
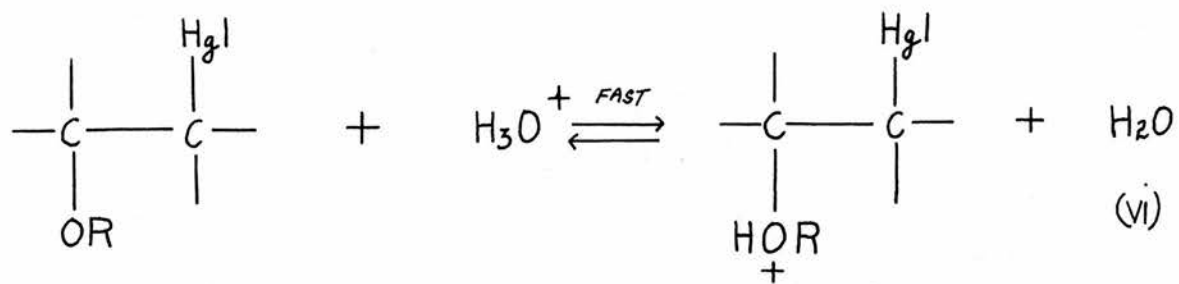
The $H_{(2)}$ resonance in the cyclohexene compound contained many unresolved lines which were thought might have been caused by $^{199}\text{Hg}-^1\text{H}_{(1)}$ coupling. The N.M.R. spectra of various sugar mercurials were examined to determine if this type of coupling was present (Part I).

Mechanism of Deoxymercuration.

Studies on the kinetics of deoxymercuration have provided additional evidence as to the trans orientation of OR and HgX groups in the olefin adducts.

A mechanism for deoxymercuration must explain the stereospecificity of the reaction and the extreme ease with which it takes place.

Wright et al²³ from kinetic studies, considered a non-ionic deoxymercuration reaction involving addition of



molecular acid to the mercurial giving a quasi ring intermediate which decomposed to the alkene.

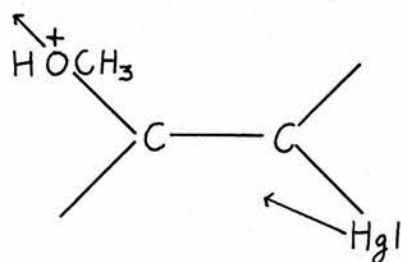
Later work by Kreevoy et al^{27,28} shows that Wright's conclusions are incorrect. The kinetics of acid catalysed deoxymercuration of the α - and β -cyclohexyl methoxymercuriodides²⁸ reveal the reaction to be first order in mercurial and in hydrogen ion and independent of the molecular acid concentration. The experimental results are consistent with the mechanism shown in equations (vi) to (viii),

The results suggest the existence of a rapid reversible protonation of the substrate. The rate-determining step then proceeds without formation of covalent bonds with the solvent, to give a mercurinium ion, which has already been proposed as the intermediate in oxymercuration. The presence of a proton in the transition state is implied by observing first order rate dependence on the acid concentration. The results are inconsistent with a general acid catalysis mechanism, which would involve proton transfer to the substrate during the rate-determining step.

Although the α - and β -mercurials have identical entropies of activation, the enthalpy of activation for the α -isomer is 8.4kcal./mole lower than for the β -isomer. In fact, the deoxymercuration of the α -compound is 10^5 to 10^7 times faster than the β -compound, depending upon the temperature of comparison. Since the starting states for both mercurials have similar structures, they probably have similar entropies.

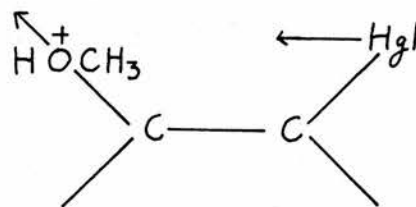
The fact that their entropies of activation are identical suggests that deoxymercuration of the α - and β -compounds proceeds by the same mechanism except that in the latter more energy is required.²⁸

The rate-determining step (vii) involves the breaking of the C—O^{H+}Me bond with simultaneous contraction of the carbon-carbon-mercury angle to form the three membered ring. For the breaking of old bonds to occur as the new bonds are formed, coplanarity of mercury, oxygen and the two carbons is required. This coplanarity can be achieved with little distortion of bond angles and slight expenditure of energy, if the mercury and oxygen groups are trans diaxially disposed. This arrangement allows atomic transitions to take place in a completely synchronised fashion without any great increase of repulsion between the non-bonded atoms (Figure I(a)).



(a)

Figure I



(b)

The formation of a diaxial intermediate from the cis isomer is unlikely because this would involve gross distortion of ring angles requiring a great deal of energy. Instead, near coplanarity of mercury, oxygen and carbon atoms is obtained with the substituents on the same side of the ring. With this arrangement it is still possible, by

having a longer carbon-oxygen bond and a larger carbon-carbon-mercury angle than in the transition state for the trans isomer, to form the three membered ring but perfect synchronisation is no longer possible (Figure I (b)). This results in the energy of the transition state for the cis isomer being greater than that of the transition state for the trans isomer, making ΔH^* for cis much higher than ΔH^* for trans.

It is clear that the mechanism proposed will accommodate the results of deoxymercuration if the α -isomer is assigned the trans configuration and the β -isomer the cis. From similar kinetic studies on the acid catalysed deoxymercuration of α - and β -cyclopentyl methoxymethylmercurials, the same result was obtained.²⁹

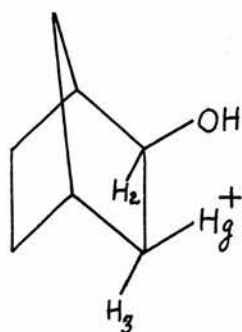
The configurational assignments of the α - and β -cyclohexyl mercurials from the kinetics of acid catalysed deoxymercuration have been confirmed by iodide ion catalysed elimination.³⁰ The application of this latter method for the determination of the stereochemistry of addition of OMe and HgX to glycals¹⁰ is discussed in Part I.

The above results provide convincing proof that for unstrained olefins both oxymercuration and the reverse reaction deoxymercuration proceed through a mercurinium ion intermediate. There are notable differences, however, between oxymercuration and other electrophilic additions, in particular, in the mode of addition to strained olefins such as norbornene.

Oxymercuration of Strained Olefins.

Wright et al¹⁴ observed that the oxymercuration of norbornene was acid catalysed giving a mercurial which had a higher dipole moment and a greater resistance to deoxymercuration than the diastereoisomer obtained by carbon-mercury epimerization. In addition, acetate ion appeared to compete with solvent as an anionic source in the reaction of norbornenes with mercuric acetate in water or methanol. This acetoxymercuration is not observed with unstrained olefins.

The profound difference in properties between the mercurials from strained and unstrained olefins suggest that the two classes differ in stereochemistry. Wright¹⁴ has argued that they have trans and cis configurations respectively. However, as noted earlier, trans addition has now been conclusively demonstrated for unstrained olefins. Traylor³¹ proposed that the addition to norbornene was exo-cis, which was confirmed by N.M.R. spectroscopy.²⁴ The spectrum of the norbornene oxymercurial gave the coupling constants:



$$J_{34} \quad 2.1 \text{ c.p.s.}$$

$$J_{23} \quad 6.8 \text{ c.p.s.}$$

The large coupling constant is in keeping with the

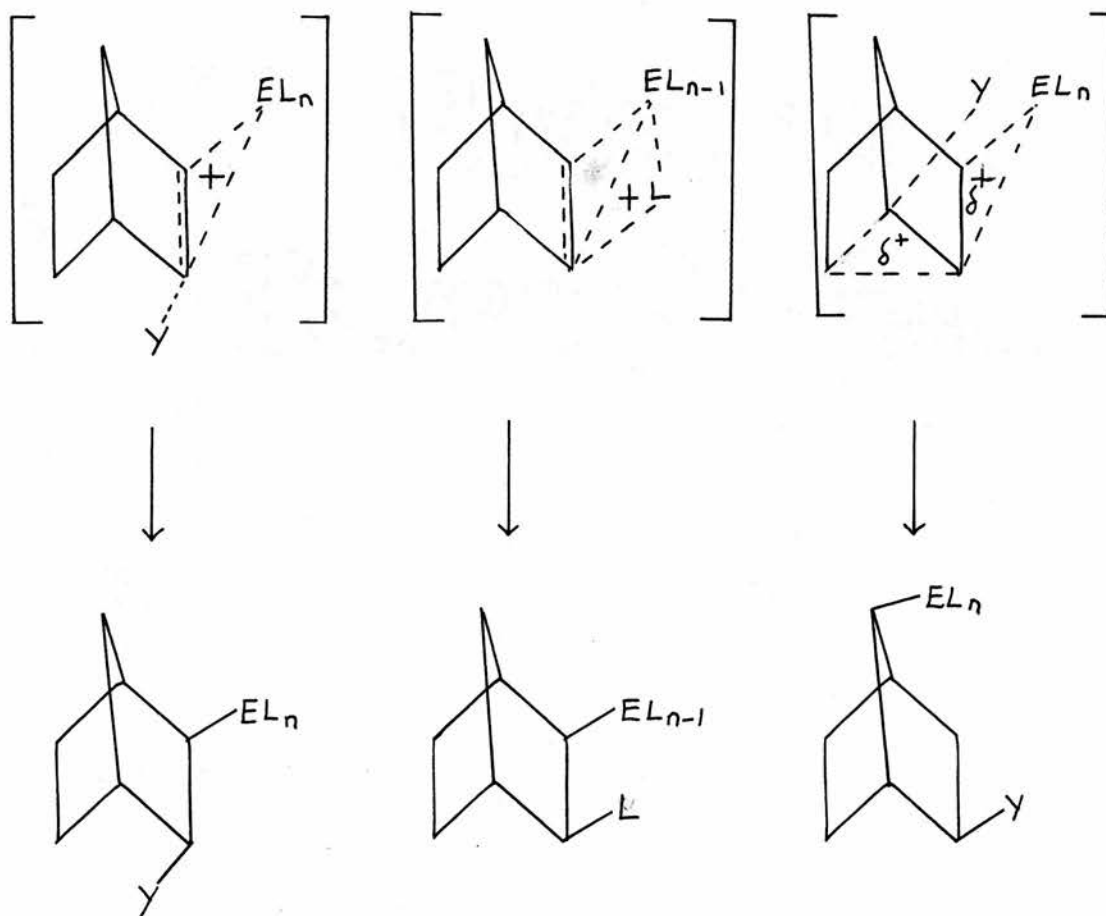
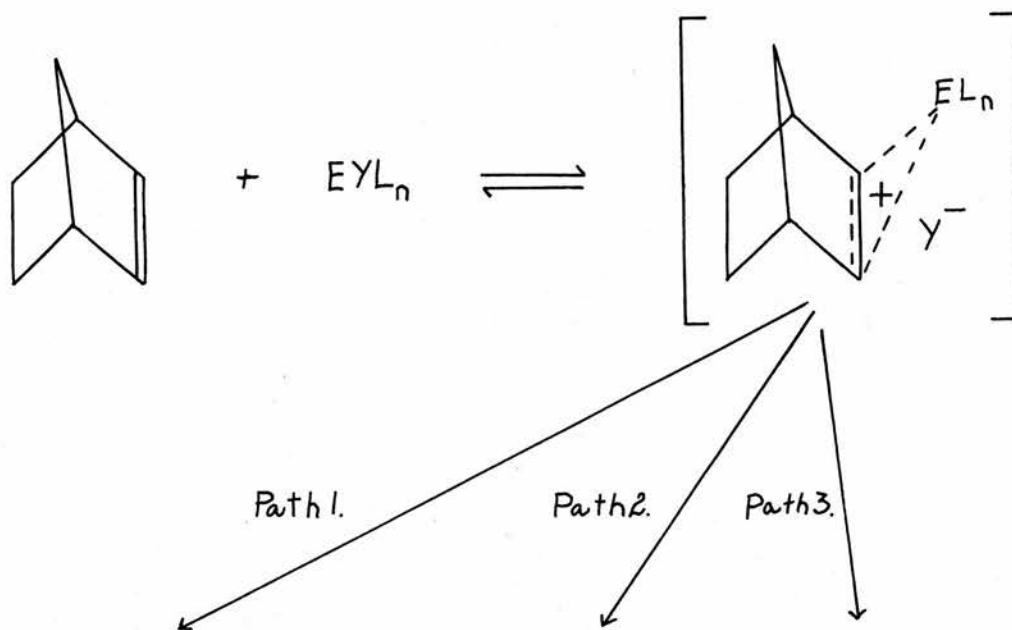
coupling constant of 7.7c.p.s. found for the cis protons in exo-norbornane diol, and 8.9c.p.s. in the endo-diol, and is much larger than for the protons in the trans diol, $J=2.3$ c.p.s. The absence of further splitting for $H_{(2)}$ is taken as proof that the hydroxyl group is exo, because $J_{12}=0$ in the exo-diol while $J_{12}=4$ c.p.s. in the endo-diol.²⁴

Traylor and Baker³² have suggested a general and more convenient method for demonstrating the stereochemical relationships of OH and HgX groups in hydroxymercurials. They observed that there was a shift of the hydroxyl stretching frequency to lower frequencies in the infrared on substitution of mercury for hydrogen β to the hydroxyl group. This shift has been attributed to some kind of electrostatic interaction between the mercury atom and oxygen. As the magnitude of the frequency shift depends upon the distance between oxygen and mercury it would be expected that the frequency shift of cis oxymercurials would be greater than trans.

The experimental results show that the cis hydroxymercurials from strained olefins have frequency shifts of -18 to -22cm.⁻¹, while hydroxymercuration products of cyclopentene, cyclohexene and aliphatic olefins have shifts of -6 to -10cm.⁻¹

The addition to norbornene of ionic reagents such as bromine, hypochlorous acid, sulphenyl chloride and peracids involves trans addition accompanied by various amounts of rearrangement.³³ Oxymercuration however gives exclusive exo-cis addition with no rearrangement.^{31,32}

17a



A general mechanism of electrophilic olefin addition has been proposed in which a π -complex in rapid equilibrium with the olefin undergoes cis or trans addition or rearrangement depending upon the electrophile and the rigidity of the olefin.^{32,33} The mechanism in which EYL_n represents the reagents, $Hg(OAc)_2$, Br_2 , $RSOCl$, $ClOH$ etc., is shown, where E is the electrophile, Y the anion and L the other ligands.

In unstrained olefins the addition proceeds via Path 1 involving backside nucleophilic attack in the usual manner. This path would become increasingly unfavoured with increasing rigidity of the olefin, because of the resistance to twist about the C—C bond required for the transition state, as shown in Figure II. Therefore increasing strain and rigidity of the olefin would favour Paths 2 and 3 over 1.

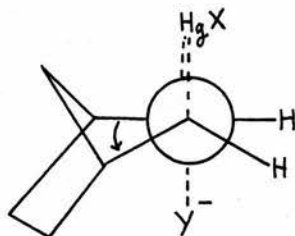


Figure II

Traylor suggests that the extent of rearrangement by Path 3 is directly related to the electronegativity of the electrophile E. Thus, increasing the C—E bond strength increases the tendency towards open carbonium ions and thus might be expected to favour rearrangement. The absence of rearrangement in norbornene oxymercuration, indicating that no carbonium ion is produced, is in keeping with the observation that butadiene oxymercuration involves

1,2 - addition.³⁴

It is interesting to note that the reaction of norbornene with lead tetraacetate in acetic acid or methanol involves extensive rearrangement,³⁵ in agreement with the greater electron affinity of tetravalent lead.

It has been found that while RS^+ and ^+HgX react with norbornene with no rearrangement, the former involves trans addition, the latter cis. The principal difference between these two groups is the ability of the mercury to carry ligands such as water, acetate etc. It is the presence of these ligands which probably causes the frontside ring opening to be more attractive than backside attack.

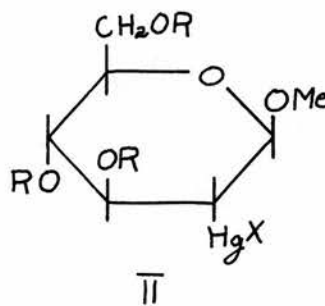
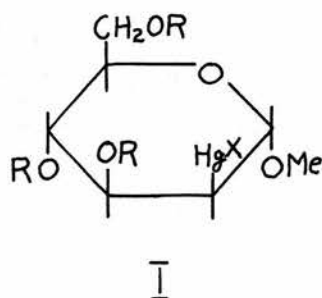
Frontside and backside opening of the mercurinium ring would be expected to become competitive with an olefin whose strain lay between that of cyclohexene and norbornene, the stereochemistry of oxymercuration then being a function of solvent nucleophilicity. It was found that such an olefin, bicyclooctene, undergoes cis and trans addition in water, a strong nucleophile, and exclusive cis addition in weakly nucleophilic acetic acid.³⁶

The object of this Introduction has been to outline briefly the oxymercuration reaction and to describe recent attempts to clarify its mechanism and stereochemistry. Now although oxymercuration addition has been applied to all manner of olefins since its discovery at the beginning of this century, it was not until 1962 that the first application

of this method to unsaturated sugar derivatives was reported independently by two sets of workers.^{10,11} The stereochemistry of oxymercuration addition to glycals and some reactions of the mercurials produced will be considered in the remainder of this thesis.

PART IThe Oxymercuration of Glycals.The Methoxymercuration of D-Glucal and its Triacetate.

It would be anticipated that the methoxymercuration of glycals would involve attachment of the mercury atom to the more nucleophilic $C_{(2)}$ atom, the OMe adding to $C_{(1)}$. Since methoxymercuration usually proceeds with trans addition then D-glucal and its triacetate would be expected to give the α -D-manno- and the β -D-gluco-mercuriglycosides (I and II).^{*} The former would be expected to predominate since it is formed by diaxial addition to the more stable half-chair conformation of the glycal.



It has been found¹¹ that the methoxymercuration of D-glucal proceeds almost stereospecifically to give a crystalline mercuriacetate. The stereochemistry at $C_{(1)}$ was established by reduction to give methyl 2-deoxy- α -D-gluco-

^{*} Note : Methoxymercuration reactions discussed in this section are shown on the flow-sheet, page 75.

pyranoside, and if trans addition is assumed, the compound must be methyl 2-acetoxymercuri-2-deoxy- α -D-mannopyranoside (I; R = H, X = OAc).

A contrary view¹⁰ of the methoxymercuration of D-glucal, involving cis addition of groups to give the β -D-manno-mercurial, is discussed later in this section.

The reaction of D-glucal triacetate with mercuric acetate in methanol,¹¹ followed by reaction with sodium chloride, gave similar amounts of two crystalline mercurichlorides. The less soluble isomer was shown by X-ray analysis³⁷ to be methyl 2-chloromercuri-2-deoxy- β -D-glucopyranoside triacetate (II; R = Ac, X = Cl). The stereochemistry at C₍₁₎ was confirmed by reductive demercuration, methyl 2-deoxy- β -D-glucopyranoside triacetate being obtained. The more soluble isomer has been assigned the α -D-manno-structure (I; R = Ac, X = Cl) because methyl 2-deoxy- α -D-glucopyranoside is obtained on reduction.

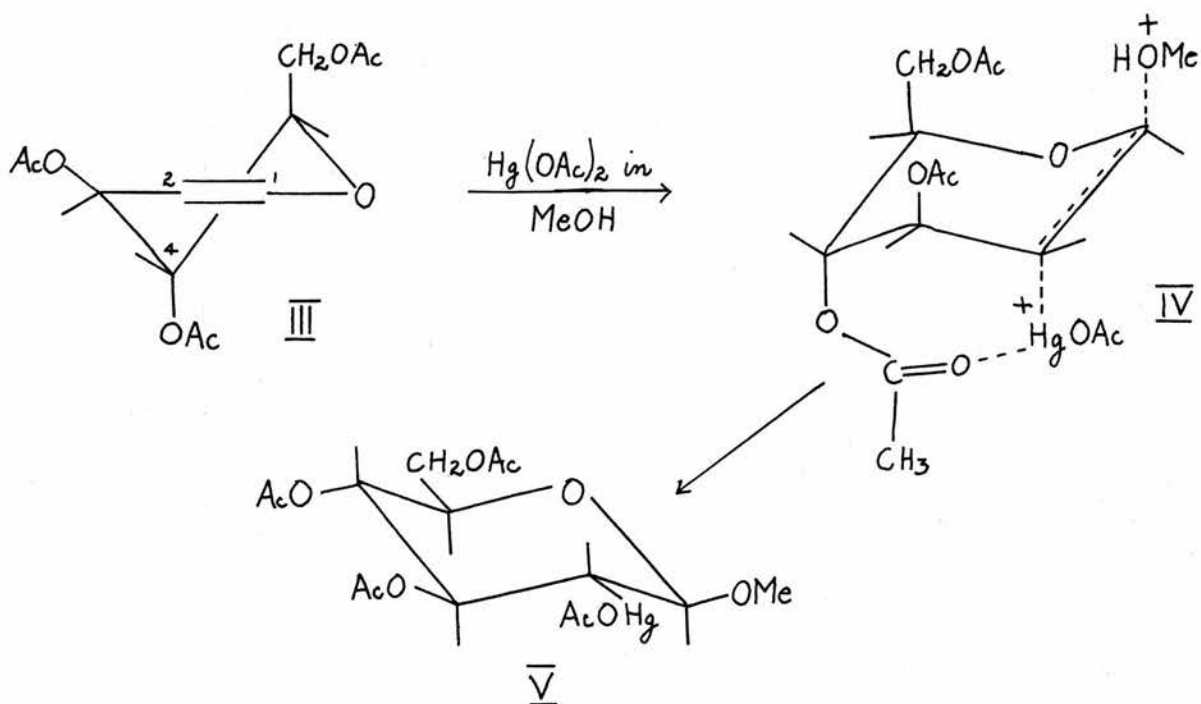
Previous attempts by Inglis³⁸ to correlate the α -glycosides from D-glucal and its triacetate by conversion of one into the other were unsuccessful. However, Manolopoulos, Mednick and Lichtin¹⁰ have reported the deacetylation of the β -D-gluco-mercurial (II; R = Ac, X = Cl) from D-glucal triacetate and the subsequent replacement of the chlorine on mercury by acetate. The application of this method to the α -D-manno-isomer (I; R = Ac, X = Cl) gave the mercuri-acetate of D-glucal (I; R = H, X = OAc) in 38% yield.

McLaren and Schwarz³⁹ were unable to obtain the α -mercuriglycoside (I; R = Ac, X = Cl) by acetylation of the D-glucal adduct (I; R = H, X = OAc) with acetic anhydride in pyridine followed by replacement with sodium chloride. Manolopoulos et al¹⁰ have had a similar failure with acetic anhydride and sodium acetate; they have suggested that a dialkyl mercury compound is perhaps produced in this acetylation. The acetylation was found to proceed smoothly, however, if the glucal adduct was converted to the mercurichloride with sodium chloride prior to treatment with acetic anhydride in pyridine, the acetylated mercurial (I; R = Ac, X = Cl) (40%) being isolated. Paper chromatography of the mother liquor showed the presence of this mercurial and a little D-glucal triacetate.

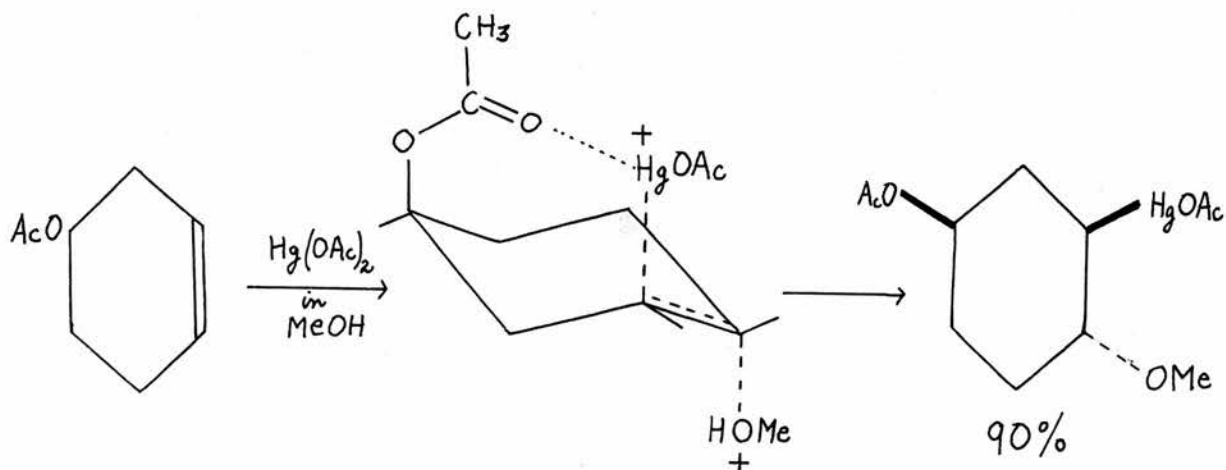
The similarity in the configurations of the mercurial from D-glucal and the α -compound obtained from D-glucal triacetate is therefore amply confirmed.

It is interesting that whereas D-glucal gives mainly the expected α -D-manno-mercurial, D-glucal triacetate (III) gives an appreciable amount of the β -D-gluco-isomer (V). The formation of the latter is unexpected since the relevant chair transition state (IV), which fulfils the stereochemical requirements of diaxial addition, must have all the substituents axial.

Henbest and his co-workers^{40,41,42} have reported that the presence in a cycloolefin of a substituent not directly



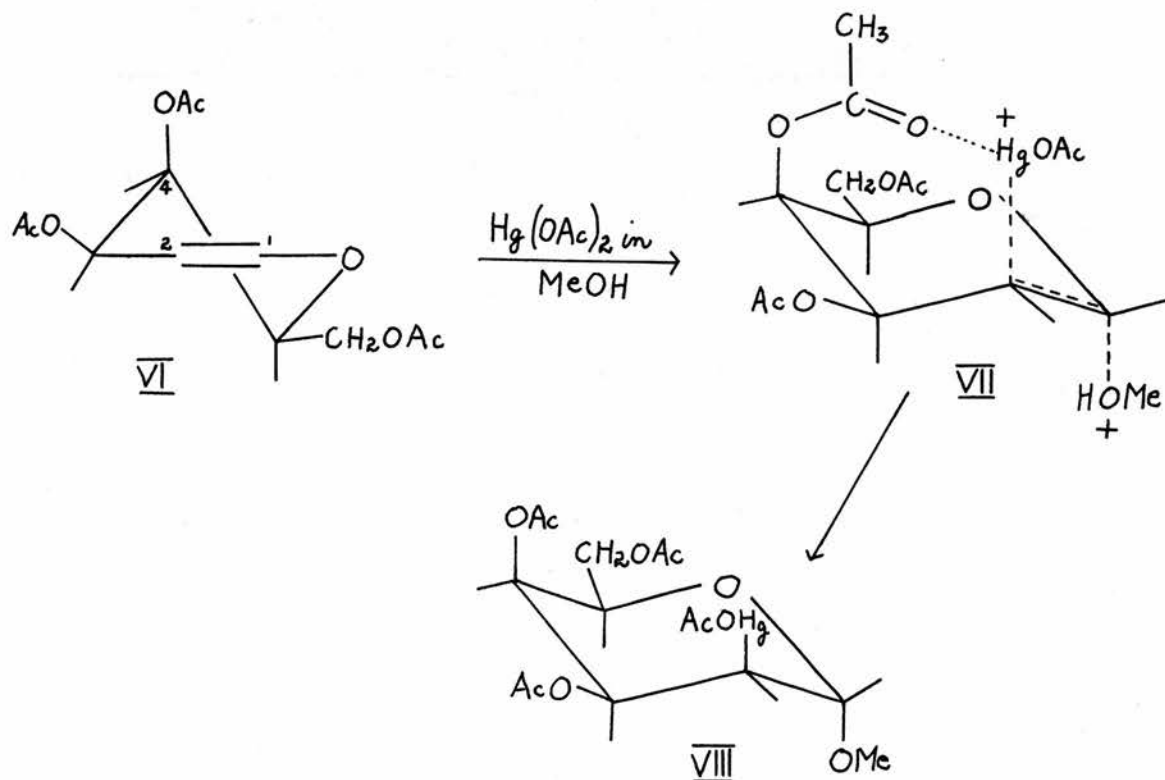
attached to the double bond can affect the direction of initial attack of the reagent adding to the double bond. Thus, the methoxymercuration of cyclohexene containing a 4-substituted Lewis base group (OH , OMe , OAc , CO_2Me , CH_2OH , CN) occurs stereospecifically to give an adduct in which the mercury is cis to the Lewis base.^{40,41} It is suggested that a cis substituted mercurinium ion is formed by partial bonding to the electron donating Lewis base group as shown below:



It might be expected, therefore, that the unfavoured transition state (IV) is stabilised by a similar complexing between the carbonyl oxygen of the 4-acetoxyl group and the mercury atom. The reason for the almost exclusive formation of the α -D-manno-isomer (I; R = H, X = OAc) in the methoxymercuration of D-glucal is probably that, as the hydroxyl group is smaller than the acetoxyl group, greater distortion of the ring angles is necessary to allow oxygen-mercury complexing to take place.

The Methoxymercuration of D-Galactal Triacetate.

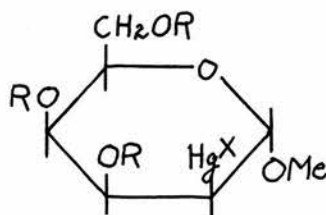
To confirm the importance of this complexing we have now examined the methoxymercuration of D-galactal triacetate (VI). Since the 4-acetoxyl group in this compound has the opposite configuration to that in D-glucal triacetate, the effect would be expected to act in the opposite sense. Hence, if complexing between the carbonyl oxygen and mercury



exists, it will fix the ring in the stereochemically favoured Cl-transition state (VII) which will result in only the α -D-talo-isomer (VIII) being produced.

The reaction of D-galactal triacetate with mercuric acetate in methanol, followed by treatment with sodium chloride, gave a crystalline mercurichloride (84%). Paper chromatography of the mother liquor showed that it contained roughly equal amounts of the above product and a second mercurial which has not been isolated, the proportion of this second mercurial must not be more than 8%.

Alkaline borohydride reduction¹¹ of the crystalline mercurial in methanol was accompanied by a great deal of elimination to the glycol. It was found that this elimination was at a minimum when the reduction was carried out in aqueous dioxan, methyl 2-deoxy- α -D-galactopyranoside (61%) being obtained. This establishes the stereochemistry at C₍₁₎ and if trans addition has taken place, the product must be methyl 2-chloromercuri-2-deoxy- α -D-talopyranoside triacetate (IX; R = Ac, X = Cl), the isomer expected on conformational grounds.

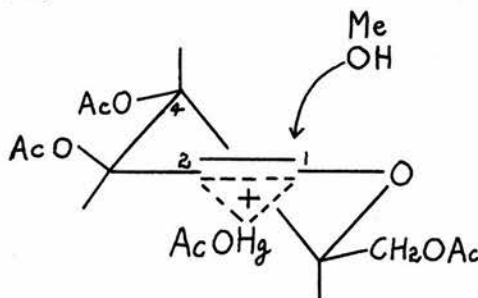


IX

Although the above complexing hypothesis provides a

satisfactory explanation of the relative proportions of the stereoisomeric products in the methoxymercuration of D-glucal, D-glucal triacetate and D-galactal triacetate, other factors may well be involved. Thus, dipolar interactions between substituent groups and the transition state, as postulated by Henbest for acyl hypohalite additions and other reactions,⁴² may play an important part not only in the present systems but also in the methoxymercuration previously studied by Henbest.^{40,41} However, such interactions are difficult to assess, particularly in the present work, since the conformational flexibility both of the ring skeleton and the substituent groups make it impossible to assign the relative directions of the various dipoles with any confidence.

A further possibility is that the formation of the β -D-gluco-isomer from the methoxymercuration of D-glucal triacetate occurs, not via the all-axial chair transition state postulated above, but via a skew conformation attained by attack of methanol on the more stable half-chair conformation of the mercurinium ion.



The formation of appreciable amounts of β -D-gluco-isomers from the Prevost reaction on D-glucal triacetate⁴³ and from

the methoxyhalogenation of this glycal,⁴⁴ may arise by a similar nucleophilic attack on the more stable half-chair conformation of the halonium ion, rather than by complexing between the attacking halogen and the carbonyl oxygen.

Examination of models suggests that the bulky axial acetate group on C₍₄₎ in D-galactal triacetate would greatly hinder the formation of the skew intermediate leading to the β -D-galacto-isomer. This is in keeping with the observed results of methoxymercuration. Since this hindrance would be less effective in D-galactal, this may explain the less complete stereospecificity of addition observed in the methoxymercuration of this glycal (see later). However, if the β -D-gluco-mercurial obtained from D-glucal triacetate has indeed been formed from a skew intermediate, then it would be expected that an appreciable amount of this isomer would also be formed in the methoxymercuration of D-glucal. Since this is contrary to the observed results, it seems more likely that the β -D-gluco-isomer arises from the all-axial chair intermediate described earlier rather than from a skew intermediate.

Comparison of the Rates of Methoxymercuration of D-Glucal and D-Galactal Triacetates.

If the formation of an appreciable amount of the β -D-gluco-mercurial in the methoxymercuration of D-glucal triacetate has occurred via the transition state (IV), this suggests that the accelerating effect of the oxygen-mercury complexing

must be considerable in order to counteract the unfavourable interactions between the three axial groups on the other side of the ring. However, in the mercuration of D-galactal triacetate, this oxygen-mercury complexing can take place when the ring is in its sterically favoured conformation (VII). It would be predicted, therefore, that D-galactal triacetate would methoxymercurate faster than D-glucal triacetate and to verify this prediction their rates of methoxymercuration were examined.

Various methods^{8,45} have been described in the literature for the determination of the rates of oxymercuration of olefins. These generally involve the estimation of unreacted mercuric acetate at intervals in the reaction, after the olefin adduct has been removed by chloroform extraction. It was decided in this case to determine the rates of methoxymercuration of the glycals using a physical method of some sort, rather than using more tedious chemical means.

A conductivity method was tried, in which the rate of the reaction was followed by observing the change in conductivity of the reaction solution on methoxymercuration. It was found that although there was a measurable conductivity change using reagents at $10^{-1}M$ concentration, the reaction was too fast to be measurable. On the other hand, when more dilute solutions were used to give a slower reaction rate, the conductivity change was barely discernible. It was decided therefore to abandon the conductivity method and

to try to make use of the changes in optical rotation on mercuration as a means of rate determination.

It is not practical to follow the reaction by observing the change in optical rotation because the reaction is too fast at the concentrations required to give a measurable rotation change. It was decided therefore to determine the relative rates of methoxymercuration of the glycols by allowing equal quantities of each glycol to compete for one molar proportion of mercuric acetate.⁴⁶ In this competition experiment the optical rotation of the solution may be regarded as being made up of the rotation contributions of unreacted D-glucal and D-galactal triacetates, and of their mercuration products. If the rotation of each of these constituents is known, it should be possible to calculate the proportion of each glycol mercurated in the competition experiment and thus their relative rates of methoxymercuration.

As detailed in the Experimental Section, measurement of the optical rotations of five easily prepared solutions showed that D-galactal triacetate methoxymercurates more than twice as fast as the glucose isomer. This supports the view that the rate of methoxymercuration of the former is enhanced by stereochemically favoured oxygen-mercury complexing.

Methoxymercuration of glycols is a very rapid process, the optical rotation of the reaction solution reaching a steady value in a matter of minutes. It was found however, that although the rotation of the competition mixture appeared

to reach a steady value after 20 minutes, on allowing the solution to stand for several weeks a slow upward drift of the rotation occurred, which was found to be caused by the presence of the unchanged glycals in the solution. The slow reactions causing this drifting of rotation were examined and elucidated, this work being described in Part III of this thesis.

It was hoped to separate and estimate by chemical means the amount of each mercurial produced in the competition experiment, and thus to confirm the polarimetric results. However, this approach was unsuccessful because the mercurials were insufficiently separated by paper, thin-layer and ion-exchange paper chromatography.

The Methoxymercuration of $\underline{\underline{D}}$ -Galactal.

The methoxymercuration of $\underline{\underline{D}}$ -galactal would be expected on conformational grounds to give the α - $\underline{\underline{D}}$ -talo-mercuriglycoside (IX; R = H), the isomer formed by diaxial addition to the more stable half-chair conformation of the glycal.

$\underline{\underline{D}}$ -Galactal was found to react rapidly with mercuric acetate in methanol and paper chromatography of the product showed that it consisted of one main constituent along with smaller amounts of other mercurials. Borohydride reduction of the crude reaction product gave methyl 2-deoxy- α - $\underline{\underline{D}}$ -galactopyranoside (28%) and some $\underline{\underline{D}}$ -galactal, but no 2-deoxy- β -glycoside could be detected (chromatography).

Although a crystalline mercuriacetate has been isolated

in poor yield from the methoxymercuration of D-galactal, it was found to be more convenient to replace ionic acetate by chloride by treatment with IRA-400 ion-exchange resin in the chloride form. A crystalline galactal mercurichloride (65%) can thus be obtained which has been assigned the α -D-talo-configuration (IX; R = H, X = Cl) because it is produced in 73% yield on deacetylation of the D-galactal triacetate mercurichloride (IX; R = Ac, X = Cl) mentioned earlier.

The Methoxymercuration of D-Lactal Hexaacetate.

D-Lactal hexaacetate contains a glycal ring identical to that of D-glucal triacetate, except that a β -D-galactosyl residue is attached to the C₍₄₎ oxygen atom. Since complexing between an acetoxyl group at C₍₄₎ and the mercury is no longer possible, it might be expected that the lactal would give one mercurial only, corresponding to the α -D-manno-isomer from D-glucal triacetate.

A syrupy product was obtained on methoxymercuration of D-lactal hexaacetate and replacement of ionic acetate by chloride failed to give a crystalline compound. Paper chromatography, using dimethyl sulphoxide as stationary phase, indicated that the mercurichloride product consisted of two mercurials in an approximate 2 : 1 ratio.

Attempts to separate these mercurials preparatively, either as mercuriacetate or chloride, using paper and thin-layer chromatography and chromatography on various ion-exchange papers, met with no success.

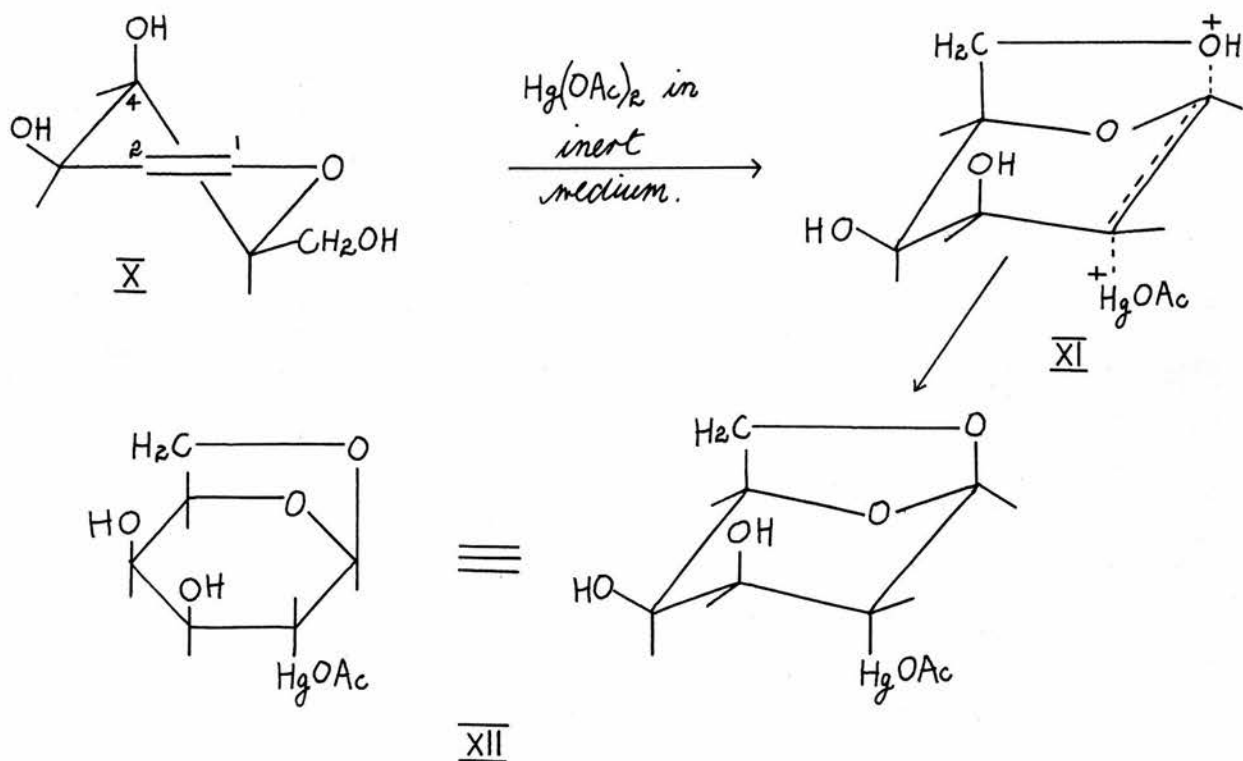
These results indicate that the methoxymercuration of D-lactal hexaacetate has not proceeded with the stereospecificity anticipated. The mercurials produced probably correspond to the α -D-manno- and the β -D-gluco-isomers from D-glucal triacetate, the isomers expected from trans addition. The formation of the β -isomer may have resulted by complexing between the mercury atom and the ring oxygen of the galactosyl residue, or with one of its acetate groups. However, other factors such as dipolar interactions between the substituent groups and the transition state may be involved and the possibility that the β -isomer is formed via a skew form (see earlier) cannot be excluded.

The Oxymercuration of D-Galactal in an Inert Solvent.

It was reported in the Introduction that mercuration in an inert solvent of an olefin containing a hydroxyl group may take place by participation of this hydroxyl group as an anionic source to give an internal ether.

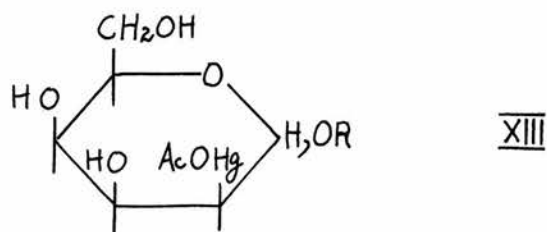
The reaction of D-galactal (X) with mercuric acetate in an inert solvent was studied in the hope that the CH_2OH group on $\text{C}_{(5)}$ would act as an internal nucleophile (XI) giving a 1,6-anhydro-sugar with mercury on $\text{C}_{(2)}$ (XII). This would provide a convenient route for the preparation of 1,6-anhydro-2-deoxy-D-galactose, which would be obtained on reduction of the adduct.

Diglyme (diethylene glycol dimethyl ether), which is a good solvent for both D-galactal and mercuric acetate, was



chosen as the inert medium. The reaction of D-galactal with mercuric acetate in dry diglyme was accompanied by a rapid rise in rotation, and after a short time a white amorphous powder was laid down. This material did not melt and was insoluble in the usual organic solvents.

Although the powder was readily soluble in water, a slow decomposition took place over several hours as was shown by the fall in optical rotation. The syrup obtained from this solution had identical chromatographic and optical rotatory properties to the product (XIII?; R = H) obtained on hydroxymercuration of D-galactal with aqueous mercuric acetate.



When the solution obtained on hydroxymercuration of galactal was titrated with alkali, two equivalents were consumed, which are attributed to the acetic acid produced on mercuration and to the titratable mercuriacetate group. However, on titration of the aqueous solution of the diglyme product, only one equivalent was consumed, presumably due to the mercuriacetate present. The fact that no acid was produced on dissolving the diglyme product in water shows that this cannot be (XIII; $R = Ac$) or a glycal-mercuric salt complex, because for each of these to give the mercuriacetate (XIII; $R = H$) acid would be produced.

The fact that 1,6-anhydro-compounds are usually strongly laevorotatory might seem to exclude structure (XII) for the diglyme adduct. However, from the Conformational Dissymmetry Rule¹ (Part IV) it would be anticipated that mercury below the ring in structure (XII) would make a strong dextrorotatory contribution to the rotation.

The rate of decomposition of the diglyme adduct in water is thought to be a function of the acid concentration, because it was found to be accelerated by acetic acid, and strongly retarded by sodium acetate. Similar effects to these have been reported in the acid catalysed deoxymercuration of acrylic esters.²¹

A possible explanation of the decomposition of the diglyme adduct in water may be that it involves conversion of the 1,6-anhydro-compound to the galactal hydroxymercuriacetate.

This conversion would involve deoxymercuration of the 1,6-anhydro-compound to the glycal catalysed by the acidic HgOAc group, followed by re-addition to give the hydroxymercurial.

The reaction of the 1,6-anhydro-compound in methanol was studied in the hope that a crystalline product would be obtained. By analogy with the decomposition in water, it might be expected that galactal methoxymercuriacetate (IX; $\text{R} = \text{H}$, $\text{X} = \text{OAc}$) would be produced, which would give the crystalline mercurichloride (IX; $\text{R} = \text{H}$, $\text{X} = \text{Cl}$) on treatment with ion-exchange resin in the chloride form. Unfortunately, however, the 1,6-anhydro-compound was found to be insoluble in this solvent.

Borohydride reduction of the 1,6-anhydro-compound was accompanied by a great deal of decomposition into galactal and 2-deoxy-galactose. Although paper chromatography showed the presence of other materials, no 1,6-anhydro-2-deoxy-D-galactose could be isolated.

Methods of Establishing the Stereochemistry of Sugar Mercurials.

1. Chemical Methods.

The method used initially in the present work to assign the stereochemistry of OMe and HgX in the glycal adducts involved establishing the stereochemistry of the methoxyl by reduction to a known deoxy-glycoside, and assuming trans addition to obtain the configuration of HgX .

Recently it has been claimed by Manolopoulos, Mednick and Lichtin¹⁰ that the methoxymercuration of D-glucal

involved cis addition giving the β -D-manno-mercurial. As this is at variance with the currently held view of trans oxymercuration, the method used by these workers to establish the stereochemistry was examined.

Manolopoulos et al¹⁰ base their conclusions on the rates of iodide-catalysed deoxymercuration. They found that the D-glucal adduct was deoxymercured appreciably slower than a variety of mercurials with trans orientation of groups, the reaction being followed by observing the time for appearance of mercuric iodide precipitate. As iodide-catalysed elimination from cis oxymercurials is appreciably slower than from trans oxymercurials,³⁰ these workers proposed a cis arrangement of groups on C₍₁₎, C₍₂₎ and C₍₃₎, and thus a β -D-manno-structure for the D-glucal adduct.

On applying this method to a variety of sugar and other methoxymercurials we were unable to duplicate these results. In no case could a precipitate of mercuric iodide be detected, although in some reactions a faint yellow colour was produced in the solution. The addition of sodium iodide to mercurichlorides was accompanied by the precipitation of sodium chloride. This replacement of chloride on mercury by iodide appears to be the main reaction taking place because cyclohexyl α -methoxymercuriodide (80%) was recovered from the reaction of the corresponding mercurichloride with ethanolic sodium iodide at 60° for 1 hour.

Further, we have found that mercuric iodide (0.1M) is

completely soluble in ethanolic sodium iodide (0.4M) giving a yellow solution; this observation throws grave doubt on the claims that mercuric iodide precipitates were produced under the conditions used by Manolopoulos *et al.*¹⁰ It seems possible that the yellow colour formed in some of the reactions may be evidence for deoxymercuration. However, the unreliability of the method is further indicated by the following observations.

While D-glucal methoxymercuriacetate gave no colouration after 1 hour with sodium iodide in ethanol at 60° , the α -D-manno-isomer from D-glucal triacetate gave a yellow solution at room temperature. Convincing chemical evidence has shown, however, that these two compounds have identical configurations.

Moreover, although a trans arrangement of groups at $C_{(1)}$, $C_{(2)}$ and $C_{(3)}$ in the mercurial from D-galactal triacetate has been established by X-ray analysis (see later), this mercurial gave no colouration on prolonged heating at 60° with sodium iodide in ethanol.

The unreliability of this deoxymercuration method as a means of establishing stereochemistry is therefore amply underlined. Indeed, it seems possible that the yellow colours observed in some cases may be caused by the presence in the sugar mercurials of traces of mercuric salts not removed by crystallisation.

It has also been claimed¹⁰ that the β -D-mannoside

structure for the D-glucal mercuration adduct is supported by the results of brominolysis. Studies on the brominolysis of 4-methylcyclohexyl mercurials have shown that replacement of the mercury by bromine proceeds with almost complete retention of configuration in a polar solvent such as methanol and with racemisation in a non-polar solvent.⁹

Brominolysis of the mercurial (II; R = Ac, X = Cl) and its deacetylated compound (II; R = H, X = Cl) with bromine in methanol gave the expected methyl 2-bromo-2-deoxy- β -D-glucopyranoside. However, similar brominolysis of the D-glucal adduct also gave this product which was thought might have resulted by isomerisation of the unstable methyl 2-bromo-2-deoxy- β -D-mannopyranoside initially formed.

Although Manolopoulos *et al*¹⁰ claim to have observed this isomerisation, it seems a rather unlikely reaction. A further disturbing feature is that a β -glycoside is formed on brominolysis of the D-glucal adduct, since Inglis, Schwarz and McLaren¹¹ have obtained methyl 2-deoxy- α -D-glucopyranoside on reduction of this mercurial with sodium borohydride. In our view, the mercurial has the α -structure and the discrepancy is to be explained in the following way. It has been found in our work on the attempted replacement of mercury in sugar mercurials by other groups (Part II) that elimination to the glycal often proceeds more readily than replacement of the mercury. Therefore, it is considered that deoxy-mercuration of the D-glucal adduct takes place on treatment

with bromine in methanol, methyl 2-bromo-2-deoxy- β -D-glucopyranoside resulting from methoxybromination of the D-glucal produced. It is of interest to note that in the methoxybromination of D-glucal triacetate with bromine in methanol, an appreciable amount of methyl 2-bromo-2-deoxy- β -D-glucopyranoside triacetate is produced.⁴⁴

2. Physical Methods.

Although trans addition has been assumed in the methoxymercuration of glycals there is no chemical evidence for this, since it is difficult to establish the stereochemistry of the mercury group by unambiguous chemical means. However, physical methods, such as X-ray analysis and N.M.R. spectroscopy, have provided convincing proof that trans addition has taken place. This work will now be considered.

(1) X-Ray Analysis.

In an attempt to establish the stereochemistry of oxymercuration addition Brook and Wright²² carried out an X-ray analysis on the α -mercurichloride obtained from the methoxymercuration of cyclohexene. Later work²³ showed that the stereochemistry of HgX and OMe groups in this compound could not be assigned with certainty from the X-ray evidence because of the failure to establish the conformation of the cyclohexane ring.

Ehrlich³⁷ has shown on the basis of X-ray evidence, that the less soluble mercuriglycoside from D-glucal triacetate had all groups equatorially attached. This establishes that

trans addition to the glycal had occurred to give the β -D-gluco-isomer (II; R = Ac, X = Cl).

The X-ray analysis of the methoxymercurichloride from D-galactal has been kindly undertaken by Dr. M. M. Harding and Miss J. Bain.

The α -glycoside structure of this mercurial has already been proved by reductive demercuration to give methyl 2-deoxy- α -D-galactopyranoside. The methoxymercuration product must therefore be the α -D-talo- or the α -D-galacto-isomer, the former being expected since it is formed by trans addition.

The crystal data for $C_7 H_{12} Cl Hg O_5$ are $M = 412$; orthorhombic; $a = 6.68$; $b = 13.6$; $c = 11.9A$; $D_{calc.} = 2.53$; $Z = 4$. The electron density projection data, which indicate that the mercury group must be axially attached to the pyranose ring, can only be satisfactorily interpreted if the adduct is assigned the α -D-talo-configuration. The results are incompatible with an α -D-galacto-mercurial in the $1C$ -chair conformation because there is no electron density in the region required for the axial CH_2OH group. In addition, the X-ray evidence suggests that there may be a bending outwards of the mercury group from the ideal axial position, resulting in a flattening of the ring.

This galactal mercurial has also been prepared by deacetylation of the methoxymercurichloride of D-galactal triacetate. Thus, X-ray analysis has established that the methoxymercuration of D-galactal and its triacetate involves

trans addition to the more stable half-chair conformations of the glycols to give α -D-talo-isomers.

(11) N.M.R. Spectroscopy.

Since chemical evidence has failed to establish the stereochemistry of the mercury group in the methoxymercurials from D-glucal and D-galactal triacetates, the N.M.R. spectra of these adducts were recorded and analysed. This work, which was kindly undertaken by Dr. A. L. Porte and Mr. K. W. Moore of the University of Glasgow, is discussed below.

The mercurials examined were methyl 2-acetoxymercuri-2-deoxy- β -D-glucopyranoside triacetate¹⁰ (II; R = Ac, X = OAc) and the corresponding mercurichloride,¹¹ methyl 2-chloromercuri-2-deoxy- α -D-mannopyranoside triacetate¹¹ (I; R = Ac, X = Cl) and methyl 2-chloromercuri-2-deoxy- α -D-talopyranoside triacetate (IX; R = Ac, X = Cl). Porte and Moore recorded the spectra with an A.E.I. R.S.2 N.M.R. Spectrometer on ca. 20% solutions of the mercurials in deuteriochloroform. In addition, we have recorded the spectra of 5% and 20% solutions of the mercurials in this solvent on a Perkin-Elmer Model R10 N.M.R. Spectrometer in order to obtain accurate values for the chemical shifts of the acetoxyl and methoxyl groups; the chemical shifts thus obtained were found to be identical for both concentrations. The spectra (Figs. 1-4) are shown at the end of this section, and the chemical shifts and coupling constants derived from these spectra are shown in Table I. The full significance of this information will now be considered.

Table I.

Chemical Shifts (τ values) and Coupling Constants (c.p.s.).

		A	B	C	D
<u>Chemical Shifts.</u>	H ₍₁₎	5.33	5.23	4.89	4.95
	H ₍₂₎	7.40	7.38	6.69	7.17
	H ₍₃₎	4.78	4.72	4.15	4.28
	H ₍₄₎	5.05	4.99	5.00	4.71
	H ₍₅₎	6.29	6.13	5.70	5.75
	H _(6A)	5.68	5.60	} 5.87 (mean)	} 5.93 (mean)
	H _(6B)	5.88	5.78		
	OCH ₃ [*]	6.47	6.46	6.63	6.63
	OCOCH ₃ [*]	7.91, 7.93 7.96, 7.97	7.91 7.95	7.88 7.94	7.75 7.94, 7.98
<u>Coupling Constants.</u>	J ₁₂	10.01	9.78	0	0
	J ₂₃	10.93	11.26	5.16	5.16
	J ₃₄	8.90	9.49	8.85	3.09
	J ₄₅	9.00	7.38	8.0	0
	J _{5A}	5.80	4.61	7.7	} 7.0 (mean)
	J _{5B}	3.23	2.78	7.9	
	J _{AB}	11.91	12.54	12.9	12.0

A=Methyl 2-acetoxymethyl-2-deoxy- β -D-glucopyranoside triacetate.B=Methyl 2-chloromethyl-2-deoxy- β -D-glucopyranoside triacetate.C=Methyl 2-chloromethyl-2-deoxy- α -D-mannopyranoside triacetate.D=Methyl 2-chloromethyl-2-deoxy- α -D-talopyranoside triacetate.

* Note : These values were determined at two concentrations on a Perkin-Elmer R10 N.M.R. Spectrometer.

An evaluation of the conformations which these mercurials assume in solution may be obtained from an examination of the magnitude of the coupling constants of the ring protons. Thus, it is possible to determine the conformations of cyclic structures by calculating the dihedral angle ϕ between protons on vicinal ring carbon atoms using the equation derived theoretically by Karplus,⁴⁷ in which the coupling constant J is related to the dihedral angle ϕ as shown below:

$$J = J_0 \cos^2 \phi - 0.28 \text{ c.p.s.}$$

$$J_0 = 8.5 \text{ for } 0^\circ \leq \phi \leq 90^\circ$$

$$J_0 = 9.5 \text{ for } 90^\circ \leq \phi \leq 180^\circ$$

From this relationship, which has come to be known as the Karplus equation, it would appear that the coupling constant J will decrease from a value of ca. 8 c.p.s. at 0° to about zero at 90° , and then increase to a value of ca. 10 c.p.s. at 180° . Experimental confirmation of this relationship has been obtained by Lemieux and his co-workers^{25,26} who found that the coupling constants for vicinal protons in diaxial ($\phi = 180^\circ$), diequatorial ($\phi = 60^\circ$) and axial-equatorial ($\phi = 60^\circ$) conformations in acetylated carbohydrates were about 8, 3 and 3 c.p.s. respectively. Although this result establishes the essential correctness of the relationship, it has been found in practice that different systems require different values of J_0 to give consistent and reasonable results. The values used here in interpreting the coupling constants of the sugar mercurials are $J_0 = 9.26$ for $0^\circ \leq \phi \leq 90^\circ$ and $J_0 = 10.35$ for $90^\circ \leq \phi \leq 180^\circ$, parameters which have already been used successfully by Hough and his

co-workers⁴⁸ to define the conformations of a variety of pyranose and furanose sugar derivatives. It was hoped by this means to calculate the dihedral angles between ring protons and thereby establish the relationship between the mercury group and the neighbouring methoxyl and acetoxyl groups in the sugar mercurials.

Examination of the Karplus equation indicates that two assignments to the dihedral angle associated with a coupling constant are possible, according to whether the coupling constant is taken to correspond to angles of less than or greater than 90° . The large coupling constants (ca. 9-11 c.p.s.) obtained for the ring protons in the mercurials (II; R = Ac, X = OAc or Cl) indicate an all-axial arrangement, i.e. $\phi = \text{ca. } 180^\circ$, of these protons in the sterically favoured Cl-chair conformation (the alternative value of $\phi = \text{ca. } 0^\circ$ is clearly excluded). This result is confirmed by examination of the chemical shifts of the methyl hydrogens of the C₍₃₎ and C₍₄₎ acetoxyl groups, the observed values of τ 7.91-7.97 being consistent with the values quoted by Hall⁴⁹ for equatorial acetoxyls (τ 7.89-7.99) and too high for axial acetoxyls (τ 7.81-7.85). Since the ring protons are therefore axially disposed, this indicates an all-equatorial arrangement of groups and hence a β -D-gluco-structure for these mercurials. This is in agreement with the structure proposed by Ehrlich³⁷ from X-ray studies.

The dihedral angles calculated from the coupling constants found for the ring protons of the α -D-talo-mercurial (IX; R = Ac, X = Cl) are shown below along with the values expected if the

mercurial existed in the Cl-chair conformation.

Ring Protons.

Dihedral Angles.

	<u>Experimental.</u>	<u>Theoretical.</u>
H ₍₁₎ , H ₍₂₎	80° or 100°	60°
H ₍₂₎ , H ₍₃₎	40° or 136°	60°
H ₍₃₎ , H ₍₄₎	52° or 125°	60°
H ₍₄₎ , H ₍₅₎	80° or 100°	60°

The values of the dihedral angles between the ring protons derived from the Karplus equation ($\phi \ll 90^\circ$) are in reasonable agreement with those expected if the mercurial had the α -D-talo-configuration. The large calculated value for the dihedral angle between H₍₁₎ and H₍₂₎ and the small value for the dihedral angle between H₍₂₎ and H₍₃₎ (as compared with the theoretical values), can be conveniently accounted for if a bending outwards of the mercury group from the ideal axial position is assumed in this mercurial, an effect which has already been predicted for the deacetylated α -D-talo-mercurial from a consideration of the X-ray evidence (see earlier).

The dihedral angles associated with the coupling constants observed for the α -D-manno-mercurial (I; R = Ac, X = Cl) are shown on the following page along with the theoretical values expected for the mercurial in the α -D-manno-configuration. Also shown are the theoretical dihedral angles to be expected if the mercurial had the α -D-gluco-configuration, i.e. the product of cis addition.

Ring Protons.Dihedral Angles.

	<u>Experimental.</u>	<u>Theoretical.</u>	
		<u>α-manno</u>	<u>α-gluco</u>
H ₍₁₎ , H ₍₂₎	80° or 100°	60°	60°
H ₍₂₎ , H ₍₃₎	40° or 136°	60°	180°
H ₍₃₎ , H ₍₄₎	7° or 160°	180°	180°
H ₍₄₎ , H ₍₅₎	19° or 154°	180°	180°

The experimental dihedral angles are in reasonable agreement with the α -D-manno-structure for the mercurial; the alternative α -D-gluco-structure appears to be unlikely on the N.M.R. evidence because of the large discrepancy observed between the experimental and theoretical values for the dihedral angle between H₍₂₎ and H₍₃₎. Confirmatory evidence for the α -D-manno-structure was obtained by comparison of the coupling constants J_{12} and J_{23} of this mercurial with those observed for the α -D-talo-mercurial above. Since these mercurials have an identical arrangement of groups on C₍₁₎, C₍₂₎ and C₍₃₎, then it would be expected that similar coupling constants J_{12} and J_{23} would be observed. The spectra show values of $J_{12} = 0$ and $J_{23} = 5.16$ c.p.s. for both compounds and this confirms that the mercurials have an identical arrangement of groups on C₍₁₎, C₍₂₎ and C₍₃₎. Since, however, the α -D-talo-structure for the methoxymercuration product from D-galactal triacetate has been proved by X-ray analysis on the product after deacetylation, this therefore confirms the α -D-manno-structure for the more soluble mercuration

product from D-glucal triacetate. Furthermore, since the structure of this acetylated α -D-manno-mercurial has been correlated by unambiguous chemical means with the methoxymercuration product of D-glucal, this confirms that the latter reaction has involved trans addition and not cis addition as proposed by Manolopoulos, Mednick and Lichtin.¹⁰

It is of interest to note here that although the $H_{(2)}$ doublet was partially hidden beneath the methoxyl peak in the spectrum of the α -D-manno-mercurial (I; R = Ac, X = Cl) in deuteriochloroform (see Figure III), this doublet was clearly discernible in the spectrum of the mercurial in benzene (i.e. $H_{(2)}$ appeared as a doublet, τ 7.15, spacing = ca. 5 c.p.s. in this solvent, the methoxyl group appearing at τ 6.97; tetramethyl silane, internal standard τ 10.00).

Since $H_{(2)}$ should assume a dihedral angle of 60° with both $H_{(1)}$ and $H_{(3)}$ in the Cl-chair conformation of the α -D-manno- and α -D-talo-mercurials, it would be expected from the Karplus equation that $J_{12} = J_{23} = \text{ca. } 3$ c.p.s. in these compounds. The observed values of $J_{12} = 0$ and $J_{23} = 5.16$ c.p.s. have already been attributed in the α -D-talo-mercurial to a distortion of the chair conformation which results from a bending outwards of the mercury group, and this explanation may equally well account for the discrepancy in the coupling constants of the α -D-manno-mercurial. It may be, however, that too much importance is being placed on the results of the Karplus equation and that some other factor may be the cause of the discrepancy observed

in these coupling constants.

Williams and Bhacca,⁵⁰ from N.M.R. studies in the steroid field, have shown that the magnitude of the coupling constants between vicinal protons is dependent upon the configuration of an electronegative group (e.g. acetate) attached to the same carbon atom as one of these protons. These workers found that in such a system, axial-equatorial vicinal proton coupling was appreciably greater (J_{ae} ca. 5 c.p.s.) with the acetate group equatorial than with the acetate group axial (J_{ae} ca. 2.5 c.p.s.). Examination of the α -D-manno- and α -D-talo-mercurials indicates that a system similar to those studied by Williams and Bhacca exists in these sugar derivatives. It would be predicted, therefore, that the coupling of $H_{(2)}$ with $H_{(3)}$, with the 3-acetate in the equatorial configuration, would be greater than the coupling of $H_{(2)}$ with $H_{(1)}$, the glycoside group being axial. This prediction is in agreement with the experimental results and this suggests that the discrepancy observed for the values of J_{12} and J_{23} in the α -D-manno- and α -D-talo-mercurials may simply be the result of this dependence of J upon the configuration of electronegative substituents. However, the possibility that this discrepancy in the coupling constants is the result of a distortion of the ring caused by a bending outwards of the mercury group cannot be excluded, particularly in view of the X-ray evidence discussed earlier.

It is of interest to note that Lemieux and his co-workers have observed that J_{23} ($H_{(2)}$ equatorial) was appreciably larger

than J_{12} in the N.M.R. spectra of methyl 2-chloro-2-deoxy- α -D-mannopyranoside⁴⁴ and methyl 2-deoxy- α -D-mannopyranoside;⁵¹ these results may be conveniently explained by assuming this dependence of the magnitude of the coupling constant upon the configuration of electronegative substituents.

The large difference observed in the chemical shifts of $H_{(2)}$ in the α -D-manno- and α -D-talo-mercurials is disturbing because these protons are in almost identical environments and similar chemical shifts would be expected. Although the structures of these compounds differ in the stereochemistry of the 4-acetoxyl group, this group is probably too remote to appreciably alter the electron field around $H_{(2)}$ by a direct effect. A more likely explanation would be that changing the stereochemistry at $C_{(4)}$ alters the conformation of the 3-acetoxyl group. Thus, examination of models suggests that changing the 4-acetoxyl group from axial to equatorial would result in a tendency of the 3-acetoxyl group to be orientated in the direction of $H_{(2)}$. Since the carbonyl group is a strongly anisotropic entity, this change in the orientation of the neighbouring acetate group might be expected to have an appreciable effect on the chemical shift of $H_{(2)}$.

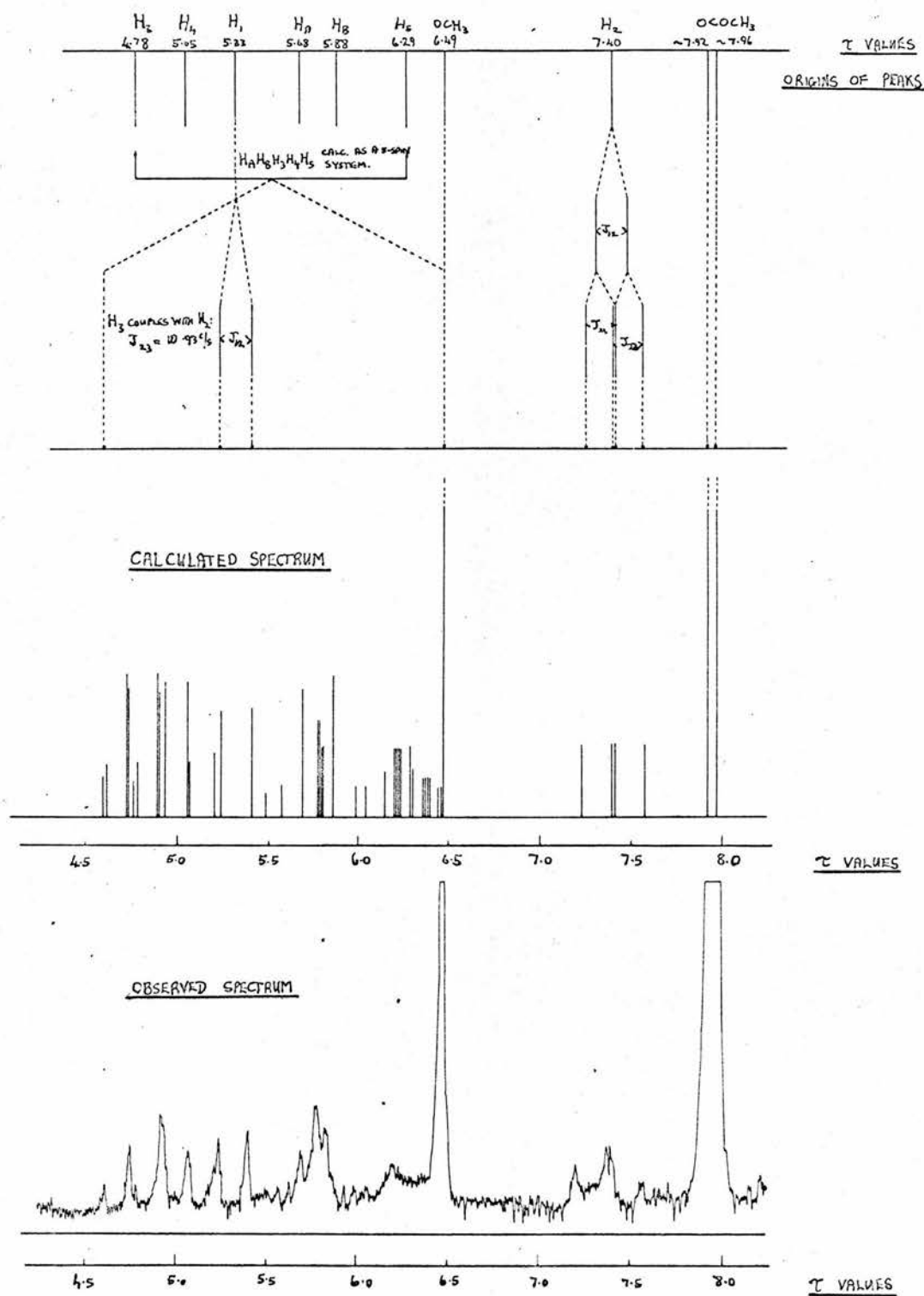
The N.M.R. spectra of the sugar mercurials were examined to ascertain whether ^{199}Hg - ^1H coupling could be detected, because the presence of such coupling in the spectrum of cyclohexyl hydroxymercuriacetate had previously been suggested by Anderson and Henry.²⁴ Although there appears to be no general agreement

on the values of $^{199}\text{Hg}-^1\text{H}$ coupling constants quoted in the literature, the most widely accepted values appear to be ca. 100 c.p.s. and ca. 130 c.p.s. for coupling of mercury with protons on the same and adjacent carbons respectively.⁵² It was found that no mercury coupling could be detected on examination of peak intensities in the regions $\frac{1}{2}-1\frac{1}{2}\tau$ (i.e. 30-90 c.p.s.) on either side of the signals of $\text{H}_{(1)}$, $\text{H}_{(2)}$ and $\text{H}_{(3)}$. This result is not altogether surprising, however, since only 16.86% of the mercury exists as the ^{199}Hg isotope and this would make $^{199}\text{Hg}-^1\text{H}$ coupling barely detectable.



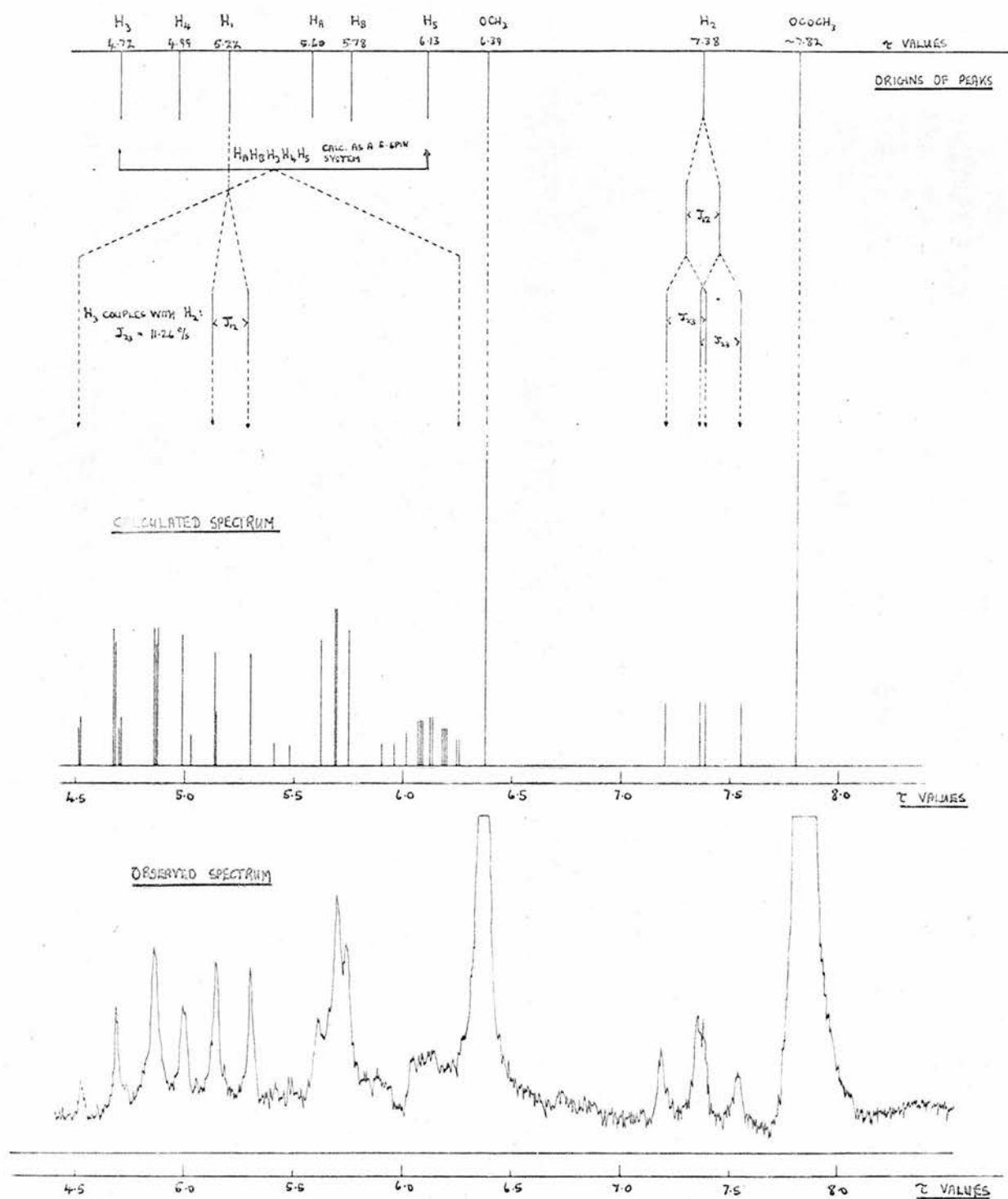
Methyl 2-acetoxymercuri-2-deoxy- β -D-glucopyranoside
triacetate.

FIGURE I.



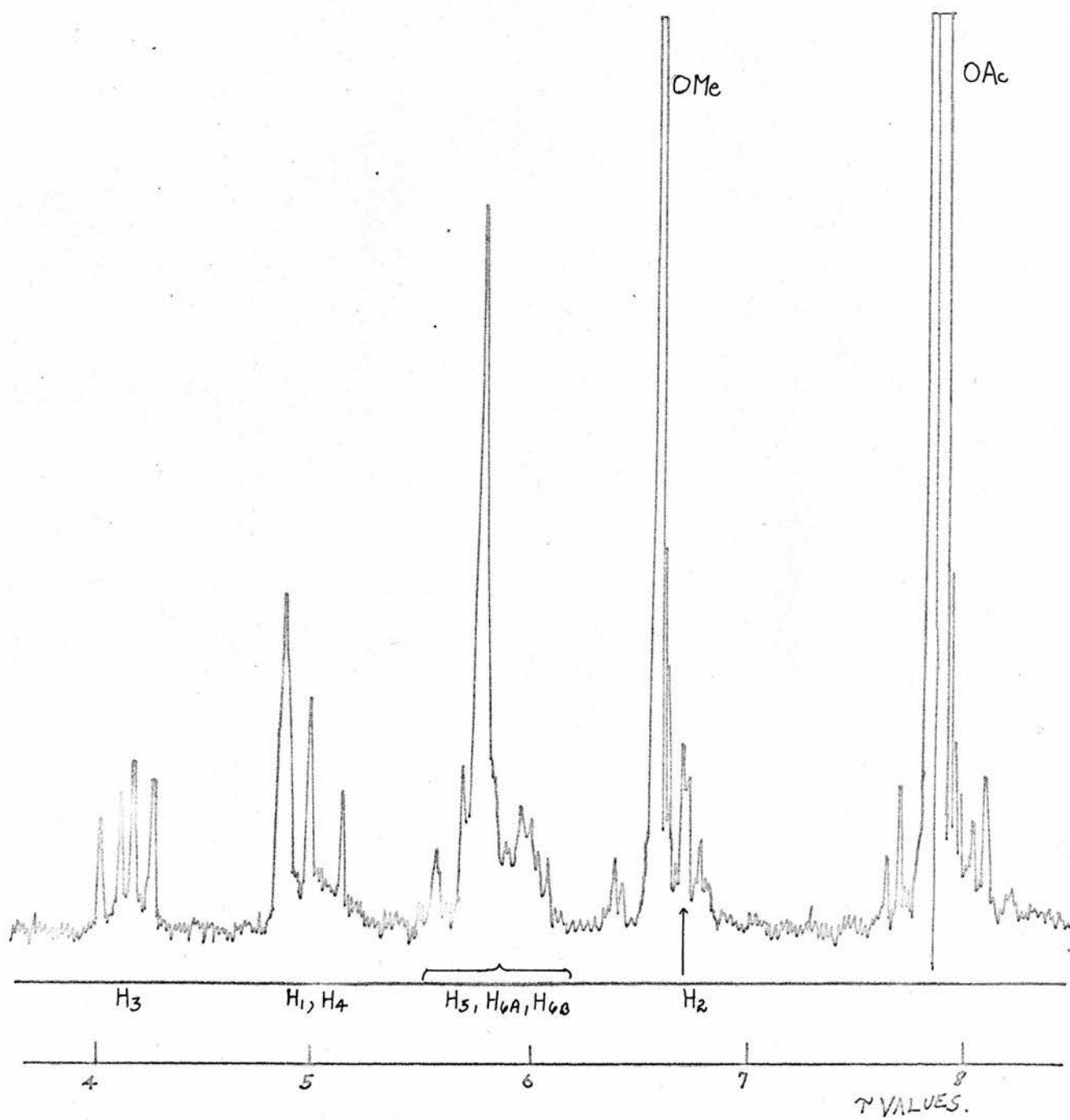
Methyl 2-chloromercuri-2-deoxy-6-D-glucopyranoside
triacetate.

FIGURE II



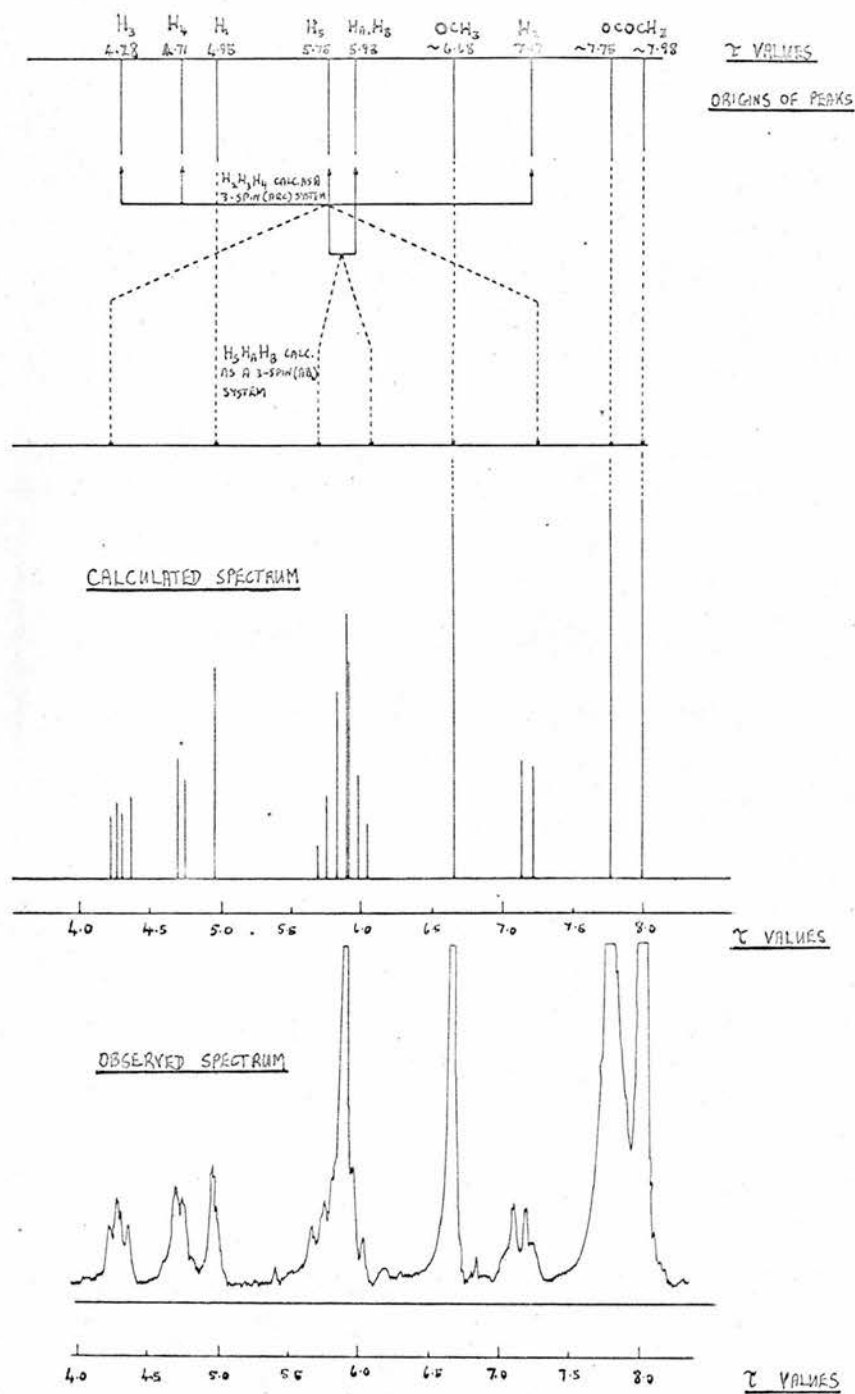
Methyl 2-chloromercuri-2-deoxy- α -D-mannopyranoside
triacetate.

FIGURE III.



Methyl 2-chloromercuri-2-deoxy- α -D-talopyranosidetriacetate.

FIGURE IV



EXPERIMENTAL1. General Information on Experimental Techniques.

Evaporation of solvents was carried out on a rotatory evaporator under reduced pressure at 40° or below. Melting points were usually determined by the capillary method on a paraffin bath, but when the amount of substance isolated was small, the Kofler block was used. Optical rotations were measured in $\frac{1}{2}$ dm., 1 dm. and 2 dm. polarimeter tubes with capacities ranging from 1 ml. to 20 ml.

Infrared spectra were determined on a Perkin-Elmer Model 137 Infracord Spectrophotometer; ultraviolet spectra on a Perkin-Elmer Model 137 U.V. Spectrophotometer, or when more accurate results were required, on a Unicam S.P. 500 Spectrophotometer. Unless otherwise stated, N.M.R. spectra were measured on a Perkin-Elmer Model R10 N.M.R. Spectrometer in deuteriochloroform and deuterium oxide solvents, and reported in τ units relative to tetramethyl silane (τ 10.00) in the former solvent, and the methyl protons of t-butanol (τ 8.80, by comparison with sodium 3-(trimethylsilyl)-1-propane sulphonate⁵³ τ 10.00⁵⁴) in deuterium oxide.

The methanol used in methoxymercuration experiments and deacetylations was dried according to Vogel's instructions.⁵⁵

Deacetylations were performed overnight using a catalytic quantity of sodium methoxide in methanol, the base being neutralised with Amberlite IRC-50 (H^+) ion-exchange

resin.

Acetylations were carried out overnight with an excess of acetic anhydride in A.R. pyridine. After decomposition of the excess anhydride by addition of water, the bulk of the reagents were removed by evaporation. The remaining pyridine and acetic acid were removed by dissolution in chloroform, and thorough washing of the organic layer with N-sulphuric acid solution followed by saturated aqueous sodium bicarbonate. In some cases the final traces of pyridine were removed by washing with a solution of cadmium chloride. The acetylated products were obtained from the dried chloroform extract by evaporation.

Paper chromatography (descending) was done on Whatman No. 1 paper, using the following solvent systems quoted as v/v:

- (i) n-butanol-ethanol-water (4:1:5, upper layer)
- (ii) methyl ethyl ketone-water (10:1)
- (iii) ethyl acetate-pyridine-water (10:4:3)
- (iv) methyl ethyl ketone-acetic acid-water (9:1:1),
saturated with boric acid

- (v) ethyl acetate-acetic acid-formic acid-water (18:3:1:4)

Solvents (i) to (v) were suitable for the separation of free sugars and glycosides.

(vi) dimethyl sulphoxide stationary phase-diisopropyl ether mobile phase.⁵⁶ This method for the separation of acetylated sugars and glycosides was modified in that after

each application of dimethyl sulphoxide in toluene, the papers were dried at ca. 80° and not at 60° as proposed by Wickberg. It was found that if the lower temperature was used the toluene was incompletely removed, which resulted in a slow travelling solvent front and a poor separation of spots. The mobile and stationary phases were removed at 120° before spraying.

(vii) dimethyl sulphoxide stationary phase-diisopropyl ether-benzene (1:1) mobile phase.⁵⁶ This system was used to separate acetylated sugar mercurichlorides.

Sprays used were:

(a) $0.5N$ -sodium hydroxide in ethanol, after passage of the paper through a dilute aqueous silver nitrate solution and drying. After the spots had developed the excess reagents were removed by dipping the paper into dilute sodium thio-sulphate solution. This spray was widely used to detect acetylated sugars and glycosides.

(b) $0.5N$ -sodium hydroxide in ethanol, after passage of the paper through a dilute solution of silver nitrate in acetone containing the minimum of water.⁵⁷ After appearance of spots the paper was treated as in (a). This spray found wide application in the detection of free sugars and glycosides.

(c) 0.04% rhodamine 6G in ethanol,¹¹ preceded by two immersions of the paper in a saturated solution of iodine in petroleum ether. This procedure showed up mercury

containing materials as bright yellow spots which fluoresced in the ultraviolet.

(d) 0.1% dithizone in chloroform. This spray showed up mercury compounds as pink spots on a blue background.

(e) a freshly prepared mixture of 4 parts of 2% sodium periodate solution with 1 part of a solution of 1% potassium permanganate in 2% aqueous sodium carbonate.⁵⁸ This spray was able to distinguish between glycals and deoxy-glycosides, the former giving instantaneous yellow spots, the latter taking 20-30 minutes to appear.

(f) a solution of 1% potassium permanganate in 2% aqueous sodium carbonate. This spray gave instantaneous yellow spots with unsaturated compounds.

Thin-layer chromatography (ascending) was done on glass plates coated with Merck Silica Gel G, the layers activated by heating at 105° for $\frac{1}{2}$ hour. Although this chromatographic method was rapid and simple to use it was not as efficient as paper chromatography for the separation of some materials. Thus, although it was possible to separate anomeric acetylated sugars and glycosides on paper using solvent (vi), these materials often travelled as one spot on thin-layer plates.

The solvent systems used in this technique depend upon the type of material being separated; the sprays used were:

(g) an ethanolic solution of anisaldehyde and

concentrated sulphuric acid (5% each, v/v).⁵⁹ This spray was used to detect all manner of carbohydrate compounds which showed up as blue spots on a pink background on heating the treated plates at 120° for 15 minutes.

Spray (d) was used to detect mercury compounds.

Ion-exchange paper chromatography provided a simple and rapid means of ascertaining whether a resin column separation would be worthwhile, and if so, suggested the resin and eluting solvent to be used. An example of the usefulness of this method in determining column conditions is reported in Part III.

Ion-exchange paper chromatography was carried out in an attempt to separate the methoxymercuration products of the competition experiment, and of D-lactal hexaacetate.

2. The Oxymercuration of Glycals and Related Reactions.

(1) Correlation of the α -Glycosides obtained from the Methoxymercuration of D-Glucal and its Triacetate.

(i) Starting from the D-Glucal Triacetate Adduct.

Methyl 2-chloromercuri-2-deoxy- α -D-mannopyranoside triacetate¹¹ (1.08 g., 2.00 mmoles) on deacetylation gave a syrupy mercurichloride; paper chromatography in solvent (i), sprays (b) and (c), indicated that only one mercurial (R_F 0.51) was present. Replacement of chlorine on mercury by acetate, by shaking with a suspension of silver acetate

(0.67 g., 4.00 mmoles) in methanol (50 ml.) for 24 hours in the dark, gave a syrup which readily crystallised. Recrystallisation from methanol gave methyl 2-acetoxymethyl-2-deoxy- α -D-mannopyranoside (0.33 g., 38%), m.p. 152° (decomp.), $[\alpha]_D^{20} +18^\circ$ (c 1 in MeOH). The mixed m.p. with a specimen prepared by methoxymercuration of D-glucal was undepressed.

(ii) Starting from the D-Glucal Adduct.

To methyl 2-acetoxymethyl-2-deoxy- α -D-mannopyranoside¹¹ (1.52 g., 3.48 mmoles) in methanol (8 ml.) was added sodium chloride (0.30 g., 5.13 mmoles) in water (1 ml.). Paper chromatography using solvent (i), sprays (b) and (c), indicated that only one mercurial was present, which had an identical R_F value to the deacetylated product from the α -D-manno-mercurial triacetate above. After removal of solvents, the product was acetylated with acetic anhydride in pyridine. It was found during working up that the optical rotation of the chloroform extract of the acetylated mercurial corresponded to an 80% formation of the α -D-manno-mercurial triacetate. Removal of chloroform gave a syrup which crystallised overnight in a desiccator. Recrystallisation from ethyl acetate-petroleum ether (60-80°) gave methyl 2-chloromethyl-2-deoxy- α -D-mannopyranoside triacetate (0.75 g., 40%), m.p. 112°, $[\alpha]_D^{20} -37^\circ$ (c 1.64 in CHCl₃). The mixed m.p. with a specimen prepared from the methoxymercuration of D-glucal triacetate was undepressed.

(2) Methoxymercuration of $\underline{\underline{D}}$ -Galactal Triacetate and Related Reactions.

$\underline{\underline{D}}$ -Galactal triacetate was prepared from acetobromo- $\underline{\underline{D}}$ -galactose,⁶⁰ m.p. 81° , by treatment with zinc and acetic acid using the procedure of Helferich, Mulcahy and Ziegler.⁶¹ The syrupy material obtained was purified by two distillations in an annular still at bath temperature $150-160^{\circ}/0.3$ mm. to give a product which crystallised after several days, m.p. ca. 30° , n_D^{18} 1.4679, $[\alpha]_D^{20}$ -15.5° (c 2.5 in CHCl_3). Overend et al⁶² report a crystalline compound, m.p. ca. 30° , n_D^{18} 1.4677, while Kuhn and Baer⁶³ obtained a syrup, n_D^{23} 1.4660, $[\alpha]_D$ -15° (c 3 in CHCl_3).

Paper chromatography in solvent (vi), spray (a), indicated that the glycal contained small amounts of acetylated $\underline{\underline{D}}$ -galactose, 2-deoxy- $\underline{\underline{D}}$ -galactose and 1,5-anhydro- $\underline{\underline{D}}$ -galactitol. These impurities could not be removed by further distillation.

(i) Methoxymercuration. The glycal (7.22 g., 26.6 mmoles) in methanol (50 ml.) was added to mercuric acetate (8.85 g., 27.8 mmoles) in methanol (115 ml.). The optical rotation rose rapidly to a constant value within $\frac{1}{4}$ hour (α in 1 dm. tube $+2.75^{\circ}$). After a further hour sodium chloride (1.60 g., 27.4 mmoles) in water (25 ml.) was added, followed by water (50 ml.). After leaving in the refrigerator overnight crystalline methyl 2-chloromercuri-2-deoxy- α - $\underline{\underline{D}}$ -talopyranoside triacetate, (7.56 g., 53%), m.p. 115° , was collected. The

mother liquor yielded identical material (4.46 g., 31%), m.p. 115° , on evaporation to half bulk. Combination of these two crops of crystals and recrystallisation from ethanol raised the m.p. to 117° , $[\alpha]_D^{23} +4^{\circ}$ (c 2 in CHCl_3) (Found: C, 29.2; H, 3.5; Cl, 6.8. $\text{C}_{13}\text{H}_{19}\text{ClHgO}_8$ requires (C, 28.9; H, 3.5; Cl, 6.6%).

Paper chromatography, using solvent (vii), spray (c), on the mother liquor from the crystalline material, showed that it contained roughly equal amounts of the crystalline mercurial and another mercurial which was not identified. The optical rotation of the syrup obtained from the mother liquor was higher than for the crystalline material which suggests that the other adduct is more dextrorotatory than the crystalline compound.

(ii) Borohydride Reduction. Methyl 2-chloromercuri-2-deoxy- α -D-talopyranoside triacetate (1.90 g., 3.52 mmoles) was dissolved in dioxan (30 ml.) containing N-sodium hydroxide solution (16 ml.). The dropwise addition of potassium borohydride (0.10 g., 1.85 mmoles) in N-alkali (11 ml.) resulted in the instantaneous deposition of mercury. After 2 hours additional borohydride (0.05 g., 0.93 mmoles) caused no further formation of mercury. The rotation of this solution corresponded to about 90% formation of methyl 2-deoxy- α -D-galactopyranoside. After removal of water by repeated evaporations with dioxan, the product was freed from inorganic salts by acetylation followed by deacetylation.

Crystallisation of the syrupy product from ethyl acetate gave methyl 2-deoxy- α -D-galactopyranoside (0.38 g., 61%), m.p. 111-112°, $[\alpha]_D^{20} +169^\circ$ (c 1 in MeOH). Literature values⁶² are m.p. 112-113°, $[\alpha]_D^{18} +170^\circ$ (MeOH). Mixed m.p. with an authentic specimen gave no depression.

The mother liquor was shown by paper chromatography using solvent (ii), spray (e), to consist mainly of the 2-deoxy- α -glycoside together with a small proportion of D-galactal.

(iii) Deacetylation. Methyl 2-chloromercuri-2-deoxy- α -D-talopyranoside triacetate (1.08 g., 2.00 mmoles) on deacetylation with a catalytic quantity of sodium methoxide in methanol gave a syrup which crystallised completely after several days in a desiccator. Recrystallisation from ethyl acetate-ethanol gave methyl 2-chloromercuri-2-deoxy- α -D-talopyranoside, (0.61 g., 73%), m.p. 137-139° (decomp.), $[\alpha]_D^{20} +52^\circ$ (c 1 in MeOH) (Found: C, 20.45; H, 3.2; Cl, 8.3. $C_7H_{13}ClHgO_5$ requires C, 20.3; H, 3.2; Cl, 8.6%).

(3) Determination of the Relative Rates of Methoxymercuration of D-Glucal and D-Galactal Triacetates by the Competition Method.

D-Glucal triacetate, m.p. 53-55°, was kindly supplied by Dr. G. R. Inglis.

All polarimeter readings were recorded at 20° in the same 2 dm. polarimeter tube, the mean of ten readings being

taken for each value. Each determination was carried out in duplicate.

The rotations of the following solutions were determined.

1. D-Glucal triacetate (0.300 g., 1.10 mmoles) in methanol (15 ml.).

Optical rotation of this solution, $\alpha_g = -0.45^\circ$.

2. D-Galactal triacetate (0.300 g., 1.10 mmoles) in methanol (15 ml.).

Optical rotation of this solution, $\alpha_{ga} = +0.16^\circ$.

3. D-Glucal triacetate (0.300 g.) in methanol (6 ml.) + 7.20 ml. 0.153M-methanolic mercuric acetate solution (0.351 g. $\text{Hg}(\text{OAc})_2$, 1.10 mmoles), the solution being made up to 15 ml.

Optical rotation of this solution, $\alpha_{gH} = -0.32^\circ$.

4. D-Galactal triacetate (0.300 g.) in methanol (6 ml.) + 7.20 ml. 0.153M-methanolic mercuric acetate solution, the solution being made up to 15 ml.

Optical rotation of this solution, $\alpha_{gaH} = +2.61^\circ$.

5. D-Glucal triacetate (0.300 g.) and D-galactal triacetate (0.300 g.) in methanol (6 ml.) + 7.20 ml. 0.153M-methanolic mercuric acetate solution, the solution being made up to 15 ml.

Optical rotation of this solution, $\alpha = +1.36^\circ$.

In the mercuration solutions, 3 and 4, the rotations reached a steady value very quickly, the values of α_{gH} and α_{gaH} being taken after 15 minutes reaction. These values did not alter on allowing the solutions to stand for several weeks.

In the competition experiment, 5, the mercuric acetate solution was added dropwise over a period of ten minutes with vigorous shaking to ensure thorough mixing of the reagents. The rotation of this solution, α , was taken when a steady value was observed (ca. 10 minutes after mixing was complete). The products in this experiment reacted further causing a slow change in the rotation over several weeks. This change, which could not be detected until several hours after mixing, was too slow to have an appreciable effect on the value of α .

It will be seen that the molarity of each glycol was the same in the solutions and that in the mercuration reactions, 3, 4 and 5, exactly one equivalent of mercuric acetate had been added.

If in the competition experiment, fraction x of D-glucal triacetate, and fraction y of D-galactal triacetate, have been mercurated, then

$$\alpha = (1 - x)\alpha_g + x\alpha_{gH} + (1 - y)\alpha_{ga} + y\alpha_{gaH} \quad (i)$$

Since only one equivalent of mercuric acetate was added, $x + y = 1$

$$\therefore y = 1 - x \quad (ii)$$

Substitution of (ii) in (i) and rearrangement gives:

$$y = \frac{\alpha - (\alpha_{gH} + \alpha_{ga})}{(\alpha_{gaH} + \alpha_g) - (\alpha_{gH} + \alpha_{ga})}$$

Let $\alpha_x = \alpha_{gH} + \alpha_{ga}$ and $\alpha_y = \alpha_{gaH} + \alpha_g$

$$\text{Then } \underline{\underline{D}}\text{-galactal triacetate mercurated} = \frac{\alpha - \alpha_x}{\alpha_y - \alpha_x} \times 100\%$$

From the values obtained in determinations, 1 to 5, above,

$$\alpha_x = -0.32 + 0.16 = -0.16$$

$$\alpha_y = +2.61 - 0.45 = +2.16$$

$$\begin{aligned} \underline{\underline{D}}\text{-Galactal triacetate mercurated} &= \frac{1.36 - (-0.16)}{2.16 - (-0.16)} \times 100\% \\ &= \underline{65\%} \end{aligned}$$

$$\underline{\underline{D}}\text{-Glucal triacetate mercurated} = \underline{35\%}$$

$$\begin{aligned} &\frac{\text{Rate of methoxymercuration of } \underline{\underline{D}}\text{-galactal triacetate}}{\text{Rate of methoxymercuration of } \underline{\underline{D}}\text{-glucal triacetate}} \\ &= \frac{\text{logarithm of fraction } \underline{\underline{D}}\text{-galactal triacetate remaining}}{\text{logarithm of fraction } \underline{\underline{D}}\text{-glucal triacetate remaining}} \quad 46 \\ &= \frac{\log_{10} 0.35}{\log_{10} 0.65} = \frac{2.5}{1} \end{aligned}$$

The validity of the above expression depends upon instantaneous mixing.⁴⁶ In order to ascertain whether mixing of the reagents was efficient in the competition experiment, determinations, 1 to 5, were repeated using 0.0367M-reagents, i.e. 1% in glycal. An identical value (2.5 : 1) for the

relative rates was obtained, which indicates adequate mixing.

Attempted Chromatographic Separation of the Mercurials from the Competition Experiment. Paper chromatography, using solvent (vii), sprays (a) and (c), on the competition mixture after addition of sodium chloride, revealed that the mercurials could only just be separated, i.e., α -D-talo-isomer, R_F ca. 0.50; α -D-manno-isomer, R_F ca. 0.44 and β -D-gluco-isomer, R_F ca. 0.38. The unchanged glycals in the solution travelled at R_F ca. 0.70. This poor resolution suggests that the separation of the mercurials on a dimethyl sulphoxide column⁵⁶ would not be practical.

The mercurichlorides travelled as one spot on Silica Gel thin-layer chromatography using ethyl acetate-diethyl ether (1 : 1) solvent, spray (d).

Chromatographic separation of the mercuriacetates in the competition mixture was also attempted on Amberlite ion-exchange papers. This technique combines the functions of ion-exchange with those of paper chromatography and in order to establish optimum conditions, a variety of papers and eluting solvents were tried. Attempted separations were performed on Amberlite WA-2 and SA-2 papers in both the hydrogen and sodium forms, and on Amberlite WB-2 paper in the hydroxide form. The solvents used were water, methanol and aqueous methanol containing varying amounts of acetic acid; sodium acetate replaced acetic acid in the eluting solvents used with papers in the sodium form. Sprays

(c) and (d) were used to detect the mercurials and spray (a) showed up the unchanged glycals.

Although it was found that the mercurials could be easily separated from the unchanged glycals on Amberlite WA-2 paper (Na^+ form) with methanol as eluting solvent, in no case could a separation of the mercuriation products be effected.

(4) The Methoxymercuration of $\underline{\underline{\text{D}}}$ -Galactal.

$\underline{\underline{\text{D}}}$ -Galactal was prepared from the crystalline triacetate by deacetylation with sodium methoxide in methanol. Recrystallisation of the crude product from ethyl acetate gave $\underline{\underline{\text{D}}}$ -galactal, m.p. $95-98^\circ$, $[\alpha]_D^{20} -20^\circ$ (c 2 in MeOH). The literature values for the physical constants of $\underline{\underline{\text{D}}}$ -galactal vary widely, the m.p. being reported as low as 90° ,⁶⁴ and as high as 112° ,⁶⁵ $[\alpha]_D$ varying from -29° (MeOH)⁶⁶ to $+5^\circ$ (MeOH).⁶² This wide range of values probably results from the failure of recrystallisation to remove the impurities present. Thus, paper chromatography using solvent (i), spray (b), on four times recrystallised $\underline{\underline{\text{D}}}$ -galactal indicated the persistence of $\underline{\underline{\text{D}}}$ -galactose, 2-deoxy- $\underline{\underline{\text{D}}}$ -galactose and 1,5-anhydro- $\underline{\underline{\text{D}}}$ -galactitol impurities. A convenient method for the complete removal of $\underline{\underline{\text{D}}}$ -galactose and 2-deoxy- $\underline{\underline{\text{D}}}$ -galactose was to percolate an aqueous solution of $\underline{\underline{\text{D}}}$ -galactal down a column of Amberlite IRA-400 (OH^-) ion-exchange resin; the glycal was easily eluted with water while these impurities were tightly held to the resin. $\underline{\underline{\text{D}}}$ -Galactal thus purified had m.p. $99-101^\circ$,

$[\alpha]_D^{20} -22^\circ$ (c 2 in MeOH).

Methoxymercuration. The addition of D-galactal (0.20 g., 1.37 mmoles) in methanol (2.5 ml.) to mercuric acetate (0.45 g., 1.41 mmoles) in the same solvent (10 ml.) was accompanied by a rise in rotation, a constant value being obtained in 5 minutes (α in 1 dm. tube $+1.84^\circ$). Paper chromatography using solvent (i), sprays (b) and (c), on a little of the crude reaction solution after addition of sodium chloride showed the presence of one mercurial (R_F 0.58) with smaller amounts of other mercury containing materials. After removal of acetic acid by repeated evaporations with methanol, the remainder of the product was converted to the mercurichloride by addition of Amberlite IRA-400 (Cl^-) ion-exchange resin. The conversion to the mercurichloride was followed by observing at intervals the disappearance of acetate ion from the reaction solution using the lanthanum nitrate spot test.⁶⁷ It was found that the small amounts of by-products adhered to the resin because evaporation of the solution after removal of resin gave a chromatographically pure syrup, which crystallised after several days. Recrystallisation from ethyl acetate-ethanol gave a product (0.36 g., 65%) with identical m.p., mixed m.p., $[\alpha]_D$ and infrared spectrum to the deacetylated mercurial from D-galactal triacetate. Therefore, the D-galactal adduct must be methyl 2-chloromercuri-2-deoxy- α -D-talopyranoside.

The α -glycoside structure was confirmed by borohydride

reduction of another D-galactal mercuration solution. Methyl 2-deoxy- α -D-galactopyranoside (28%) was obtained after freeing from inorganic salts by acetylation followed by deacetylation. Paper chromatography using solvent (ii), spray (e), on the mother liquor showed the presence of methyl 2-deoxy- α -D-galactopyranoside and D-galactal, but no deoxy- β -glycoside could be detected.

(5) The Methoxymercuration of D-Lactal Hexaacetate.

The glycal, m.p. 117° , was kindly supplied by Professor E. L. Hirst.

The addition of D-lactal hexaacetate (1.12 g., 2.00 mmoles) in methanol (50 ml.) to mercuric acetate (0.063 g., 2.08 mmoles) in methanol (10 ml.) was accompanied by a rapid rise in rotation (α in 2 dm. tube $+0.31^{\circ}$). Evaporation gave a syrupy mercuriacetate product, which was converted with sodium chloride (0.12 g., 2.08 mmoles) to the mercurichloride (1.40 g.). The mercuriacetate and the mercurichloride products resisted all attempts at crystallisation. Paper chromatography, solvent (vii), sprays (a) and (c), on the mercurichloride product showed that it contained two mercurials (R_F ca. 0.30 and ca. 0.35), the faster moving being the main product. These materials could not be separated by thin-layer and ion-exchange paper chromatography.

(6) The Oxymercuration of D-Galactal in Diglyme.

Diglyme (diethylene glycol diethyl ether; B.D.H. Ltd.) was purified by drying over sodium wire and distillation

over sodium. Diglyme thus treated gave no evidence of a water peak in the N.M.R. spectrum of the neat material; this method was a simple and rapid means of detecting small amounts of water, 0.1% being easily detected.

(i) Oxymercuration. D-Galactal (0.37 g., 2.57 mmoles) in diglyme (25 ml.) was added to mercuric acetate (0.85 g., 2.67 mmoles) in the same solvent (20 ml.). The optical rotation of the solution rose to a strong positive value (α in 2 dm. tube $+2.50^\circ$), the reaction appearing complete after 5 minutes. About 15 minutes after mixing of the reagents the reaction solution went opalescent and a white precipitate was laid down. After allowing the reaction solution to stand at room temperature overnight, the white amorphous material was collected by filtration and washed free of diglyme with diethyl ether. This solid (0.80 g.), which did not melt but slowly darkened above 160° , could not be purified by recrystallisation because of its insolubility in the usual organic solvents. The material gave, $[\alpha]_D^{20} +51^\circ$ (5 minutes) $\longrightarrow +18^\circ$ (ca. 12 hours) (c 2.16 in H_2O), ν_{max} . 1600 and 1320 $cm.^{-1}$ (ionic acetate absorption bands¹⁰) (Found: C, 22.9; H, 3.3. 2-Acetoxymercuri-2-deoxy-1,6-anhydro-D-galactose, $C_8H_{12}HgO_6$ requires C, 23.8; H, 3.0%). The low carbon content may be due to the presence of mercuric salt in this crude product.

The final value for the specific rotation of the aqueous solution above corresponded exactly to the specific rotation

of the syrupy mercuriacetate (XIII; R = H) obtained by treatment of D-galactal with aqueous mercuric acetate. Paper chromatography, using solvent (i), sprays (b) and (c), on the aqueous decomposition solution of the diglyme adduct after addition of sodium chloride, alongside galactal hydroxymercurichloride, showed that both products were identical (R_F 0.36). This confirms that the diglyme adduct is decomposed in water to give 2-acetoxymercuri-2-deoxy-D-talose (XIII; R = H).

Thin-layer chromatography, spray (d), on the aqueous solution of the diglyme product alongside 2-acetoxymercuri-2-deoxy-D-talose with iso-propanol-ethyl acetate (1 : 1) containing 1% acetic acid,⁶⁸ and on the mercurichlorides using ethanol-benzene (1 : 1) solvent, also suggested that these materials were identical.

(ii) Borohydride Reduction. As the diglyme adduct decomposed in water, the reduction was carried out by addition of the solid in small amounts to potassium borohydride in aqueous alkali, decomposition thus being kept to a minimum. Removal of solvents, followed by acetylation and deacetylation, gave a non-crystallisable syrup, which was shown by paper chromatography using solvent (i), spray (b), to contain D-galactal, 2-deoxy-D-galactose and several other materials, one of which (R_F 0.38) may be 1,6-anhydro-2-deoxy-D-galactose.

(7) Deoxymercuration Experiments.

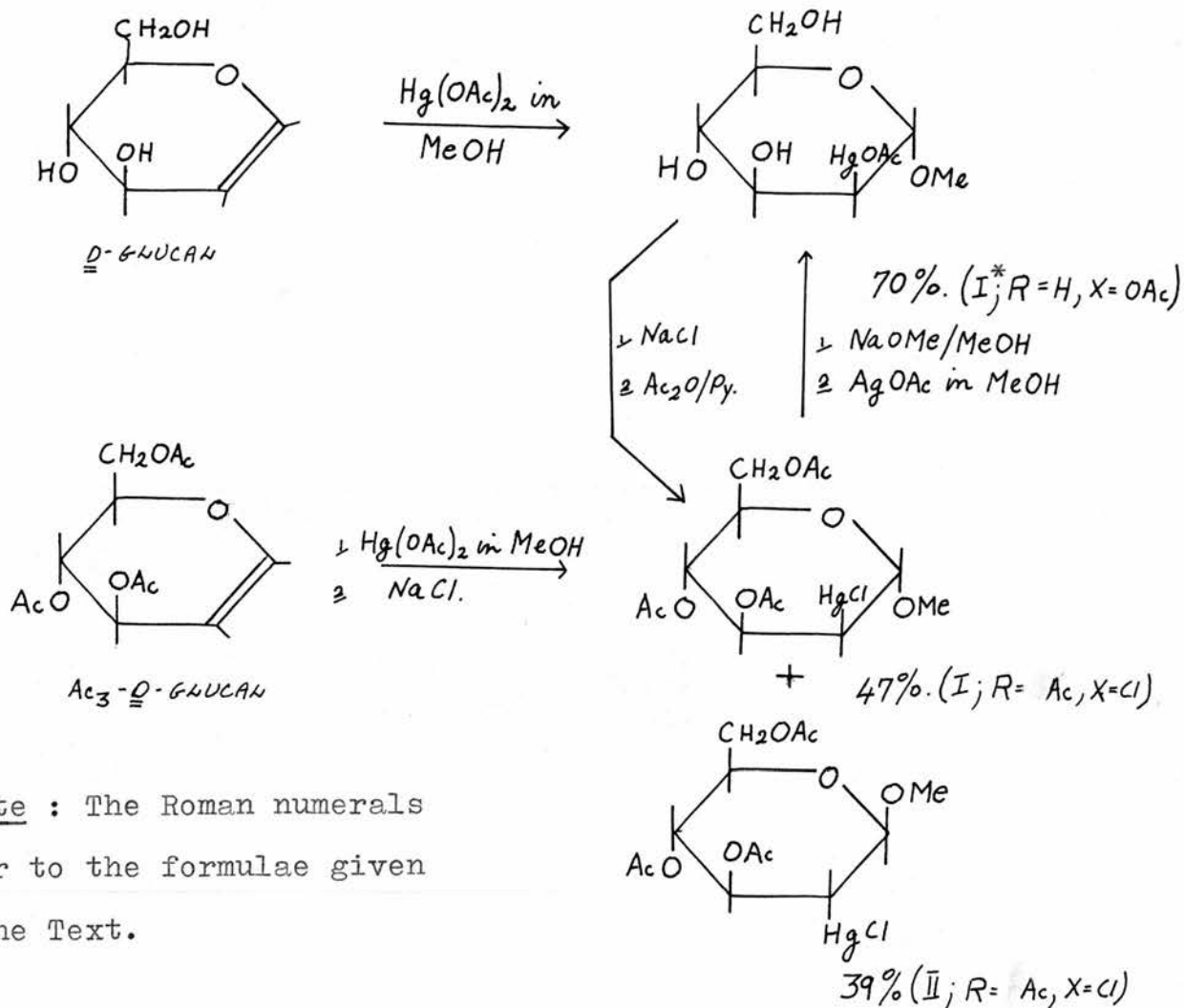
The mercurials were purified by recrystallisation before use.

The reactions were performed according to the procedure of Manolopoulos, Mednick and Lichtin.¹⁰ This involved the addition of sodium iodide (4 mmoles) to each mercurial (1 mmole) in ethanol (10 ml.), the solutions being heated on a water bath at 60°. Contrary to the observations of these workers, we were unable to detect a precipitate of mercuric iodide in any of the reactions.

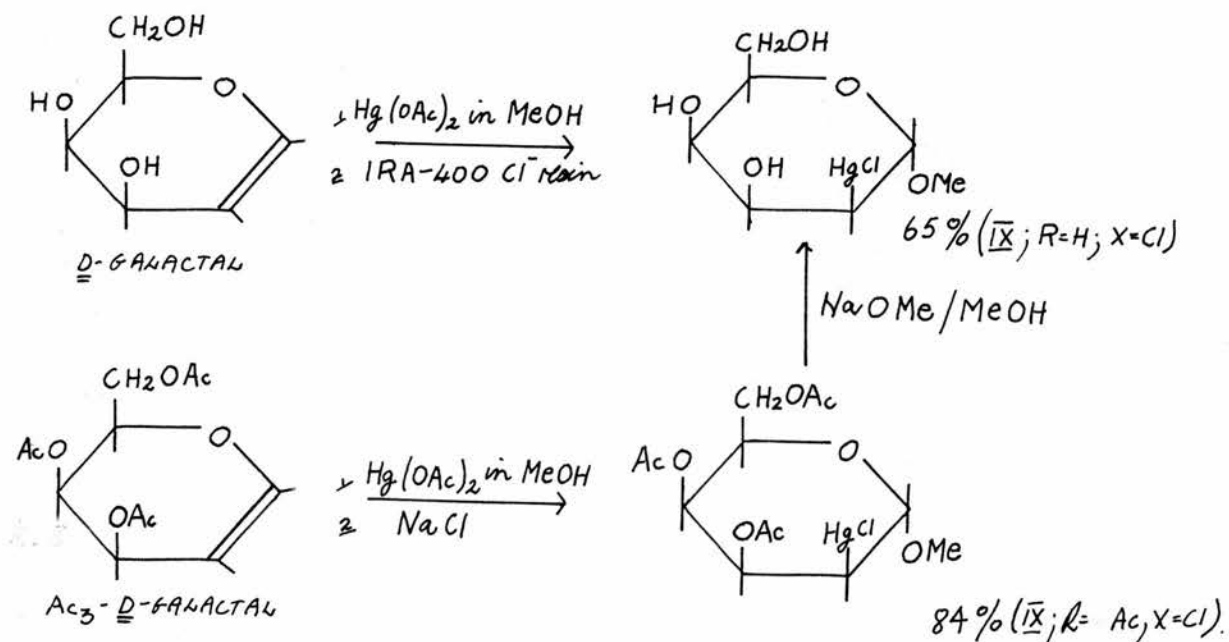
The addition of sodium iodide to solutions of methyl 2-chloromercuri-2-deoxy- α -D-mannopyranoside triacetate, methyl 2-chloromercuri-2-deoxy- β -D-glucopyranoside triacetate and cyclohexyl α -methoxymercurichloride resulted in the immediate deposition of sodium chloride, the solutions assuming a faint yellow colouration almost immediately. The intensity of the colour was not increased appreciably by heating the reaction solutions at 60° for 1 hour. Addition of water to the reaction solution of the cyclohexene adduct resulted in an 80% recovery of the mercurial as the mercuri-iodide.

Methyl 2-chloromercuri-2-deoxy- α -D-talopyranoside triacetate and the methoxymercuriacetate of D-glucal gave no yellow colouration on heating with sodium iodide in ethanol at 60° for 1 hour. A colour was produced, however, on boiling the solutions for several minutes.

Methoxymercuration Reactions discussed in Part I.



* Note : The Roman numerals refer to the formulae given in the Text.



PART II

A. The Attempted Replacement of Mercury in Sugar Mercurials
by Other Groups.

The methoxymercuration of glycals provides a convenient route for the preparation of glycosides containing a mercury group on C₍₂₎. The possibilities of replacement of the mercury group in these adducts were investigated and this work will now be considered.

The replacement of mercury by halogen and hydrogen has already been mentioned in the Introduction and Part I of this thesis. In this section will be described the attempted introduction of acetoxyl and nitroso groups into position 2 of the pyranose ring by the replacement of the mercury group in sugar methoxymercurials by treatment with lead tetraacetate and nitrosyl chloride reagents respectively.

The Attempted Replacement of Mercury by Acetoxyl by Treatment
with Lead Tetraacetate.^{69,70}

The attempted replacement of mercury by acetoxyl in the methoxymercuration products from D-glucal triacetate by treatment with lead tetraacetate, was carried out in acetic acid, a weakly polar solvent. It was hoped that the replacement would proceed by a free radical mechanism under these conditions, involving loss of configuration at C₍₂₎ to give methyl α-D-mannopyranoside and glucopyranoside tetraacetates. A similar replacement of

mercury by bromine in 4-methylcyclohexyl mercurials by treatment with bromine in acetic acid has been reported as proceeding by a free radical mechanism to give a mixture of similar amounts of the cis and trans isomers.⁹

Methyl 2-chloromercuri-2-deoxy- α -D-mannopyranoside triacetate (I; R = Ac, X = Cl) was treated with lead tetraacetate in acetic acid at 60°. The reaction, which was followed by observing both the change in optical rotation and the uptake of lead tetraacetate, was complete after 2 hours, one mole of lead salt being consumed. Paper chromatography on the syrupy reaction product after freeing from inorganic salts indicated that the mercurial had been completely decomposed. The product consisted of several mercury-free materials, none of which corresponded to methyl α -D-glucopyranoside or mannopyranoside tetraacetates expected from the replacement of mercury by acetoxyl. The low methoxyl content of the product suggested that the chief reaction occurring under these conditions was deoxymercuration of the mercurial to give the corresponding glycal, D-glucal triacetate; the products obtained were thought to have resulted from the reaction of lead tetraacetate with this glycal. This was confirmed by the reaction of D-glucal triacetate with lead tetraacetate in acetic acid, identical products to the above being obtained (paper chromatography) (Part II, B).

The low mobility of the products on dimethyl sulfoxide paper chromatography⁵⁶ suggested that they were partially

acetylated sugars. This was confirmed by deacetylation, which gave D-mannose together with a little D-glucose, while acetylation gave crystalline α -D-mannose pentaacetate and small amounts of the β -D-mannose and β -D-glucose pentaacetates.

The deoxymercuration of the mercurial may be catalysed either by acetic acid or the $^+\text{Pb}(\text{OAc})_3$ ion,⁷⁰ or both. To ascertain whether acid catalysed deoxymercuration was significant, the reaction of methyl 2-chloromercuri-2-deoxy- α -D-mannopyranoside triacetate (I; $\text{R} = \text{Ac}$, $\text{X} = \text{Cl}$) with acetic acid at 60° was studied. A slow decomposition took place over ca. 4 hours as was shown by the rise in optical rotation. Paper chromatography on the product showed that the mercurial had been completely decomposed, and that several mercury-containing materials were present. No D-glucal triacetate could be detected in the reaction products.

This decomposition in acetic acid may involve acid catalysed deoxymercuration of the mercurial, followed by acetoxymercuration of the glycal produced. This explanation would account for the rise in optical rotation during the decomposition and the absence of glycal in the product. Since the products of this reaction were of no great interest to us, they were not investigated further.

Since the decomposition of the mercurial occurs twice as fast in acetic acid containing lead tetraacetate than in acetic acid alone, this would suggest that $^+\text{Pb}(\text{OAc})_3$ ion catalysed deoxymercuration plays a significant part in the

former reaction.

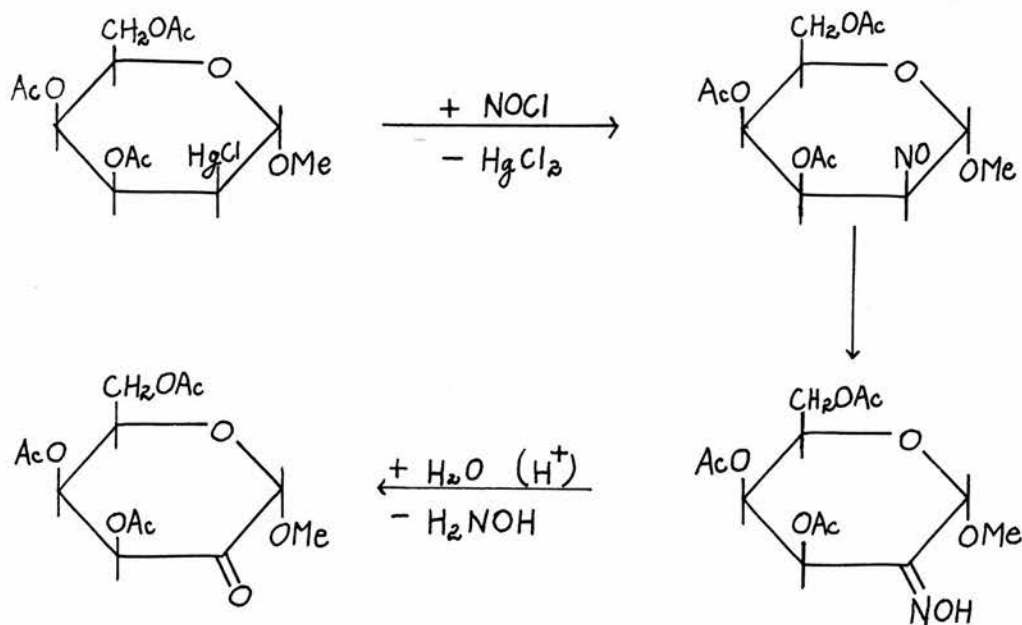
As mentioned in the Introduction, a trans diaxial disposition of OMe and HgX groups in a mercurial is the ideal arrangement for deoxymercuration.^{28,29} Since this arrangement exists in the stereochemically favoured 1C-chair conformation of methyl 2-chloromercuri-2-deoxy- α -D-mannopyranoside triacetate (I; R = Ac, X = Cl), this might explain why deoxymercuration and not replacement of mercury by acetoxyl has occurred on treatment of this mercurial with lead tetraacetate in acetic acid. However, in methyl 2-acetoxymercuri-2-deoxy- β -D-glucopyranoside triacetate (II; R = Ac, X = OAc),¹⁰ a trans diaxial arrangement of these groups can only be attained when the mercurial is in the stereochemically unfavourable 1C-chair conformation. It might be expected, therefore, that deoxymercuration of the β -D-glucomercurial would not occur as readily as for the α -D-manno-isomer. Thus, in the reaction of the former with lead tetraacetate in acetic acid, the replacement reaction might now be more favourable than the elimination.

Methyl 2-acetoxymercuri-2-deoxy- β -D-glucopyranoside triacetate (II; R = Ac, X = OAc) reacted more slowly than the α -D-manno-compound (I; R = Ac, X = Cl) with lead tetraacetate in acetic acid at 60°, one mole of lead salt being consumed in ca. 4 hours. Paper chromatography on the reaction product showed that it consisted of partially acetylated sugars identical to those obtained from the α -D-mannomercurial; no

glycoside tetraacetates were present. This was confirmed by deacetylation which gave only D-mannose and a little D-glucose while acetylation gave their pentaacetates.

The above results indicate that deoxymercuration proceeds much more readily than the replacement of mercury by acetoxyl under the conditions of the experiment. The ease with which sugar methoxymercurials eliminate to the glycal indicates their unsuitability as starting materials for the preparation of 2-substituted glycosides. This point is amply underlined on attempting the replacement of mercury by a nitroso group. The Attempted Replacement of Mercury by Nitroso by Treatment with Nitrosyl Chloride.

Smith and Taylor⁷¹ have reported that the general reaction of polymethylphenyl mercuriacetates with nitrosyl chloride in chloroform gave the corresponding nitroso compounds in good



yields. The reaction of nitrosyl chloride with a sugar mercurial was studied in the hope that a similar replacement might occur, and thus provide a convenient route for the preparation of 2-keto-glycosides as shown.

The mercurial used in the reaction was methyl 2-chloro-mercuri-2-deoxy- α -D-talopyranoside triacetate (IX; R = Ac, X = Cl) and the nitrosyl chloride reagent was prepared in situ by the decomposition of n-butyl nitrite with hydrogen chloride in chloroform, or in a second experiment was used as a solution of the gas in a suitable organic solvent. The reaction, which was carried out at room temperature or below, was accompanied by the precipitation of mercuric chloride. Introduction of the nitroso group into the pyranose ring did not occur under these conditions, however, because the reaction product gave a negative Lassaigne test for nitrogen. From a consideration of the decomposition of the sugar mercurials with lead tetraacetate in acetic acid described earlier in this section, it might be expected that deoxymercuration was the reaction occurring under these conditions. This was confirmed by examination of the reaction of cyclohexyl α -methoxymercuri-chloride with nitrosyl chloride in dichloromethane, cyclohexene being shown by gas-liquid chromatography to be the chief constituent of the reaction product.

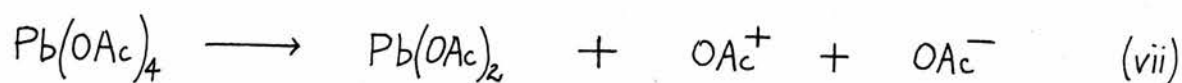
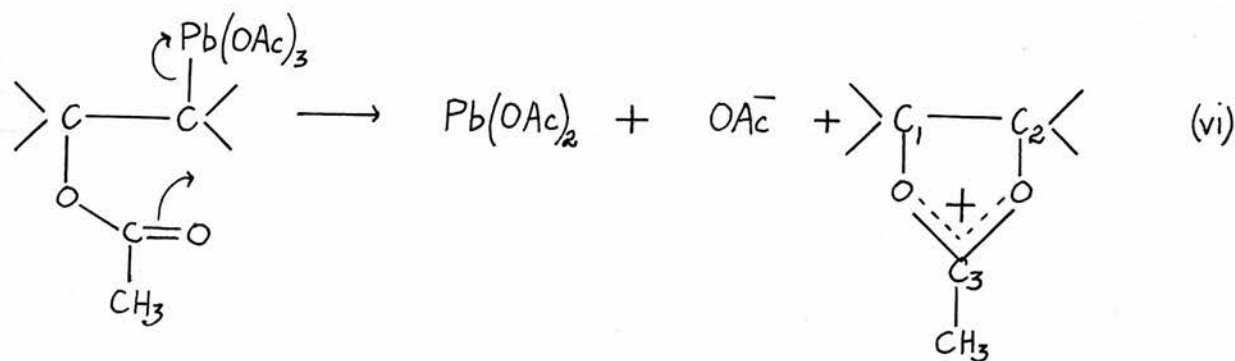
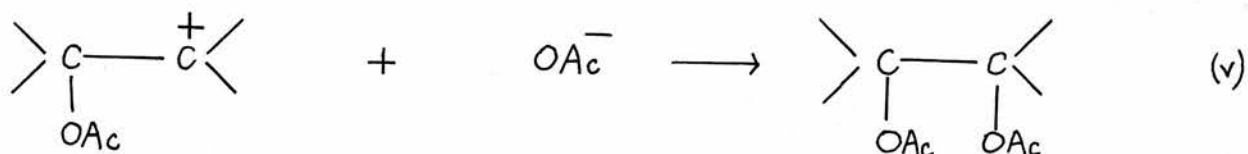
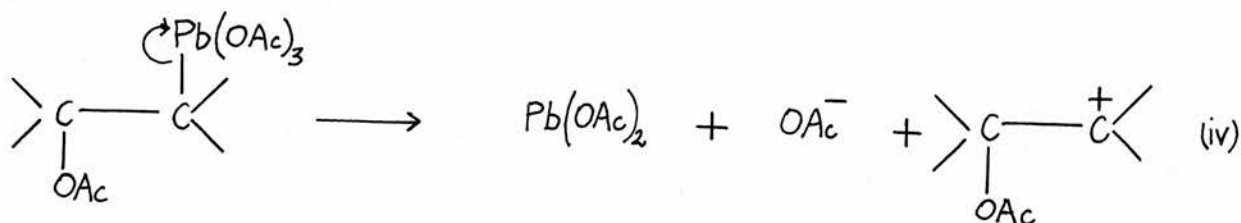
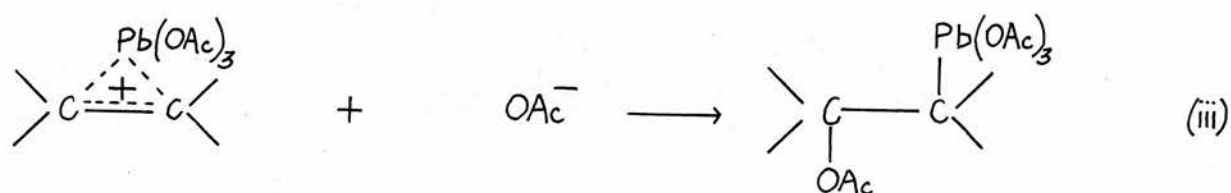
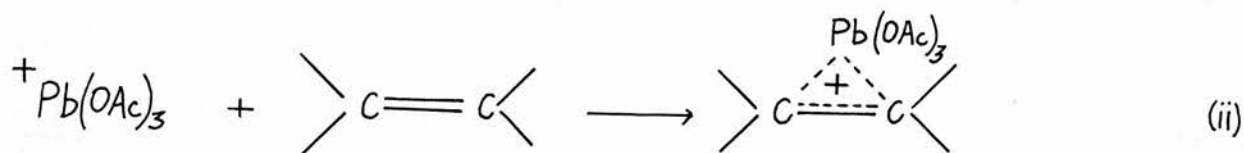
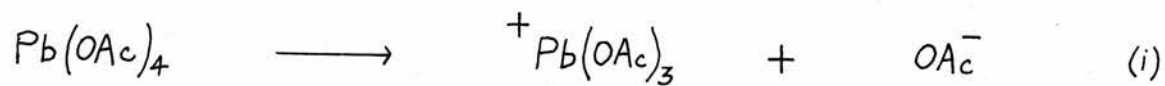
B. The Reaction of $\underline{\underline{D}}$ -Glucal Triacetate with Lead Tetraacetate in Various Solvents.

Acetic Acid.

As mentioned earlier in this section, the decomposition of methyl 2-chloromercuri-2-deoxy- α - $\underline{\underline{D}}$ -mannopyranoside triacetate (I; R = Ac, X = Cl) and methyl 2-acetoxymmercuri-2-deoxy- β - $\underline{\underline{D}}$ -glucopyranoside triacetate (II; R = Ac, X = OAc) with lead tetraacetate in acetic acid was thought to involve an initial deoxymercuration of the mercurials to give $\underline{\underline{D}}$ -glucal triacetate. It was suggested that the products obtained from these mercurials had resulted from further reaction between the glycal and lead tetraacetate. This suggestion is now confirmed by examination of the products from the reaction of $\underline{\underline{D}}$ -glucal triacetate with lead tetraacetate in acetic acid.

Criegee⁷⁰ has reported that the reaction of ethyl vinyl ether with lead tetraacetate in acetic acid involved the addition of two acetate groups. Since glycals behave like simple vinyl ethers in most addition reactions, it might be expected that the reaction of $\underline{\underline{D}}$ -glucal triacetate with lead tetraacetate in acetic acid would involve addition of two acetate groups to give $\underline{\underline{D}}$ -mannose and $\underline{\underline{D}}$ -glucose pentaacetates.

The reaction of $\underline{\underline{D}}$ -glucal triacetate with lead tetraacetate in acetic acid at room temperature was found to be complete after 4 days, 1 mole of lead salt being consumed. The product was shown by paper chromatography to consist of several



materials with identical R_F values to those obtained from the reactions of the mercurials with lead tetraacetate. There was no suggestion of any pentaacetates of D-glucose or D-mannose being present. The product was shown to consist of partially acetylated sugars because deacetylation gave only D-mannose and a little D-glucose, while acetylation gave crystalline α -D-mannose pentaacetate together with small amounts of β -D-mannose and β -D-glucose pentaacetates. The reaction of D-glucal triacetate with lead tetraacetate must therefore have involved the addition of hydroxyl and acetoxyl to the double bond, and not two acetoxyl groups as expected from Criegee's work.^{69,70}

The mechanism, (eqns. i - v), proposed by Criegee^{69,70} for the addition of two acetate groups to olefins by treatment with lead tetraacetate, is shown opposite.

This mechanism involves the ionisation of lead tetraacetate to give a triacetoxylead cation (eqn. i) which adds to the olefin (eqn. ii) to give a cyclic intermediate similar to the mercurinium ion of oxymercuration addition. Ring opening by acetate (eqn. iii) gives an unstable lead adduct which decomposes into a carbonium ion (eqn. iv). Neutralisation of this carbonium ion by acetate gives the diacetate product (eqn. v).

The extensive rearrangement which has been observed in the reaction of lead tetraacetate with olefins such as norbornene³⁵ and p-methoxystyrene⁷⁰ is strong evidence for

the existence of a carbonium ion intermediate.

Criegee^{69,70} has suggested, however, that the diacetate product may also be achieved via an acetoxonium ion intermediate. This would be formed by participation of a neighbouring acetoxyl group in the decomposition of the unstable lead adduct as shown in equation (vi). Backside nucleophilic attack on the acetoxonium ion by acetate gives a trans diacetate product.

Mosher and Kehr⁷² proposed that the acetoxonium ion can be attained directly by attack on the double bond of an acetate cation which they suggest is produced by equation (vii).

The addition of hydroxyl and acetoxyl to the double bond to give partially acetylated sugars is strong evidence for an acetoxonium ion having been produced in the above reaction of the glycal. Winstein and his co-workers^{73,74} studied reactions involving the formation of acetoxonium ion intermediates and showed that a complete change in the course of the reaction was effected by the presence of traces of water in the acetic acid solvent. Thus, decomposition of an acetoxonium ion occurs by backside nucleophilic attack by acetate at $C_{(1)}$ and $C_{(2)}^*$ in anhydrous acetic acid to give trans diacetates. In moist solvent, however, the greater reactivity of $C_{(3)}^*$ over $C_{(1)}$ and $C_{(2)}$ becomes the dominant

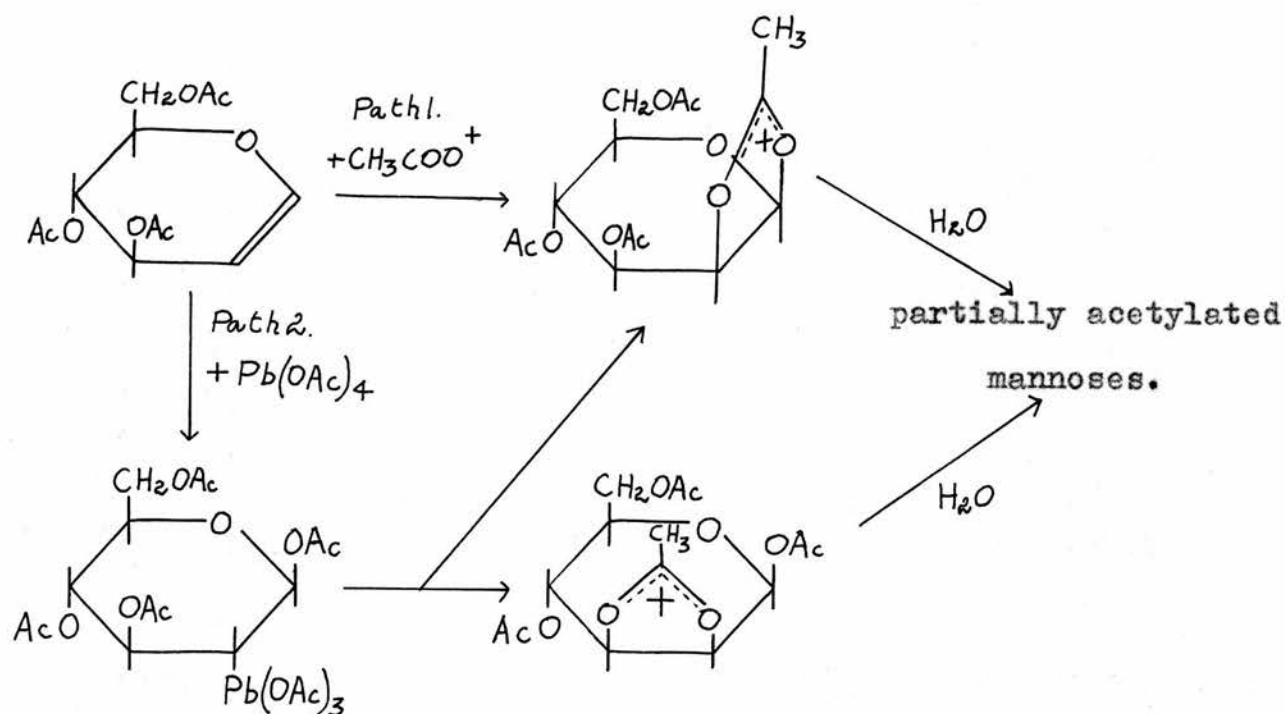
* Note : These subscripts refer to the numbering of the acetoxonium ion shown in equation (vi).

factor resulting in addition of water to that position followed by frontside ring opening to give cis glycol monoacetates.

The molarity of the glycol in our reaction with lead tetraacetate was ca. 0.03M, the acetic acid used being of A.R. quality which may contain up to 0.4% water, i.e. ca. 0.22M.

Lemieux and Ciper⁷⁵ studied the decomposition, via an acetoxonium ion, of 1,2-orthoacetates of α -D-glucopyranose triacetate with acetic acid containing varying amounts of water. These workers found that when the water content of the acetic acid was equimolar to the orthoester, frontside ring opening of the acetoxonium ion occurred quantitatively to give α -D-glucopyranose tetraacetate. It would appear, therefore, that the water content in the above reaction of D-glucal triacetate with lead tetraacetate in acetic acid would be more than sufficient to decompose the acetoxonium ion intermediate to give partially acetylated products.

The partially acetylated mannose derivatives which are the predominant product in the reaction of the glycol with lead tetraacetate must be derived from an intermediate in which the acetoxonium ring lies above the pyranose ring. As mentioned earlier, this intermediate could be formed by direct attack on the glycol of acetate cation (Path 1), or by the addition of lead tetraacetate followed by decomposition of the unstable adduct assisted by participation of a neighbouring acetoxyl group as an internal nucleophile (Path 2).



If the reaction had occurred by Path 2 then it might have been expected, by analogy with the methoxymercuration of D-glucal triacetate,¹¹ that addition of lead tetraacetate to give a lead derivative with the α -D-manno-configuration would also have occurred, resulting in the formation of an appreciable proportion of glucose derivatives. However, it has been found that the acetylated reaction product contained ca. 85% α -D-mannose pentaacetate.

Winstein and his co-workers⁷⁴ have reported that decomposition of an acetoxonium ion in anhydrous acetic acid, with or without acetate salt being present, gives trans diacetates. It might be expected, therefore, that on repeating the reaction of the glycol with lead tetraacetate under anhydrous conditions, addition to give α -D-mannose and β -D-glucose pentaacetates would occur.

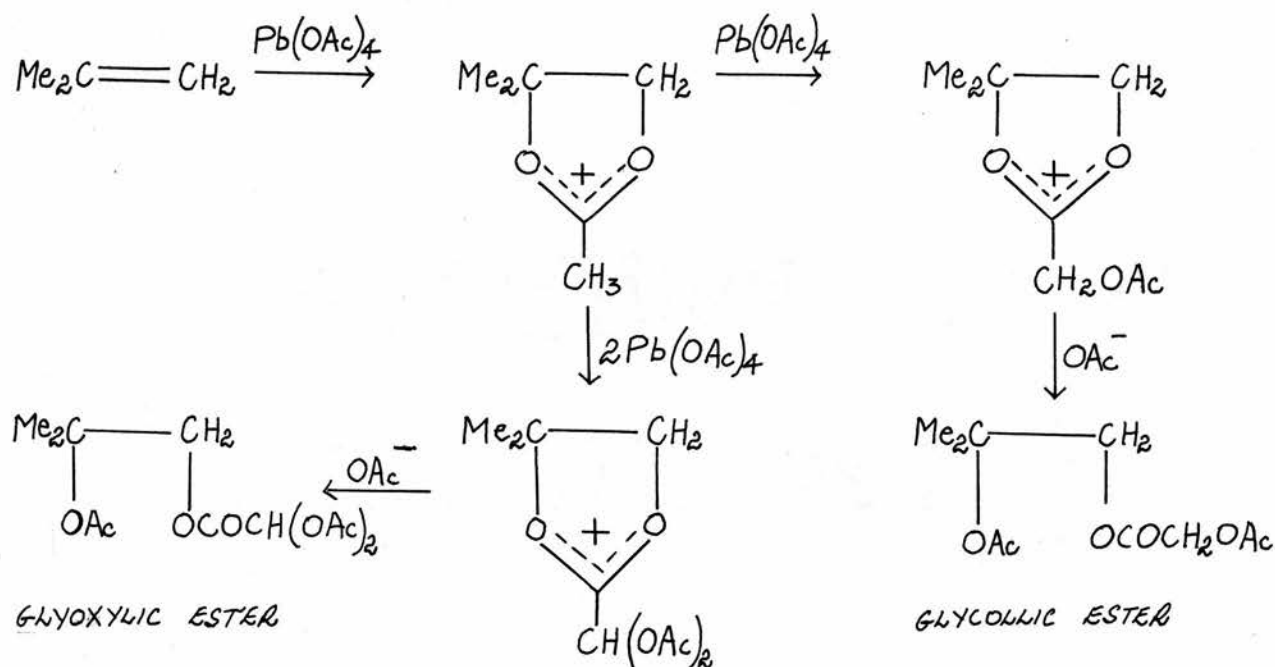
Anhydrous Acetic Acid.

The reaction of D-glucal triacetate with lead tetraacetate was repeated in A.R. acetic acid, which had been dried by distillation from boron triacetate.^{76,77} A different reaction to that in moist solvents occurred under these anhydrous conditions, two moles of lead tetraacetate being consumed. Paper chromatography on the product after removal of lead salts indicated that numerous materials were present, none of which corresponded to the expected glucose and mannose pentaacetates. Although the products travelled very slowly on dimethyl sulphoxide paper chromatography, they were not partially acetylated sugars because little change was effected on acetylation. Chromatography on the deacetylated product showed the presence of mannose together with small amounts of glucose and several other materials, which were not identified.

Although Winstein and his co-workers⁷⁴ have reported that acetate salt is not necessary under anhydrous conditions to form trans diacetates, it was decided to repeat the above reaction in the presence of sodium acetate in the hope that pentaacetates would be produced. It was found that two moles of lead salt were consumed and although paper chromatography on the product suggested that small amounts of pentaacetates were present, the chief reaction products appeared to be the slow moving materials as before.

Criegee⁶⁹ has reported that in the presence of an excess

of lead tetraacetate, diacetate addition to olefins may be complicated by oxidation of the methyl group of the acetoxonium ion intermediate. Thus, in the reaction of isobutene with excess lead tetraacetate in the absence of water (i.e. under conditions in which the acetoxonium ion is stable), esters of glycollic and glyoxylic acids were produced;



it seems possible that similar reactions occur in the present case.

In an attempt to keep unwanted reactions to a minimum and therefore favour pentaacetate formation, equimolar quantities of glycol and lead salt were allowed to react. It was found that under these conditions no pentaacetate was formed, the product consisting of the materials encountered above together with unchanged glycol.

The above results indicate that the reaction of D-glucal

triacetate with lead tetraacetate in anhydrous acetic acid does not involve simple addition of two acetoxyl groups. To ascertain whether the reaction occurring under these conditions involved oxidation of the acetoxonium methyl group, the reaction of β -D-glucose pentaacetate with lead tetraacetate in anhydrous acetic acid was studied. Lemieux and Brice,⁷⁸ from studies on the rates of acetate exchange between D-glucose pentaacetates and stannic trichloride acetate, have reported that the β -D-glucose pentaacetate undergoes acetate exchange via an acetoxonium ion intermediate. Thus, if the glycal reaction involves oxidation of the methyl group of the acetoxonium ion, then a similar oxidation might occur with β -D-glucose pentaacetate under the same conditions. This was not found to be the case, however, because the pentaacetate was recovered unchanged after prolonged heating with the lead salt under anhydrous conditions. This result suggests that the complication occurring in the glycal reaction is not caused by oxidation of the acetoxonium methyl group. This was confirmed by examination of the N.M.R. spectrum of the product from the reaction of the glycal with lead tetraacetate in anhydrous solvent.

Since the methylene protons in the proposed glycollic ester oxidation product are in a similar environment to the methylene protons in acetylglycollic esters, $\text{CH}_3\text{CO}_2\text{CH}_2\text{CO}_2\text{R}$, it would be expected that the signals of these two sets of protons would have similar τ values.

Ethyl acetylglycollate was prepared by the acetylation of ethyl glycollate with acetic anhydride in pyridine. Analysis of the N.M.R. spectrum of this material in deuteriochloroform indicated that the methylene protons appeared as a sharp singlet at τ 5.40. However, the reaction product from the glycol showed only a weak signal at this τ value. If this signal corresponds to the methylene protons of a glycollic ester, then the proportion of this oxidation product in the reaction product must be small.

The above results show that the reaction of D-glucal triacetate with lead tetraacetate in anhydrous acetic acid does not involve simple addition of acetate groups or acetoxylation of an acetoxonium ion intermediate. The exact nature of the reaction occurring under these conditions remains in doubt.

Anhydrous Benzene.

Benzene has been used as an alternative solvent for olefin-lead tetraacetate reactions. Thus, Criegee⁷⁰ has reported that the reaction of ethyl vinyl ether with lead tetraacetate in benzene gave ca. 90% of the diacetate adduct.

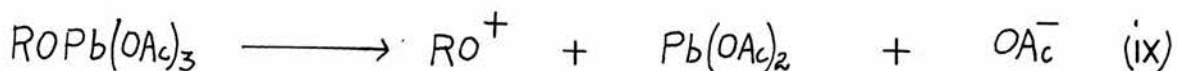
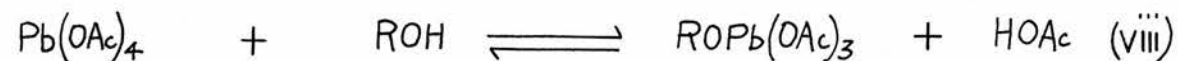
The reaction of D-glucal triacetate with lead tetraacetate in anhydrous benzene was studied to discover whether addition occurred under these conditions. Since the reaction was slow at room temperature it was necessary to heat the reaction solution at 60°, two moles of lead salt being consumed after 8 hours. The syrupy product obtained after removal of

inorganic salts was chromatographically identical to the product obtained using anhydrous acetic acid as solvent. Once again, no pentaacetates could be detected. Deacetylation of the reaction product gave mannose together with small amounts of glucose and several other materials, while acetylation caused little change in the pattern of spots on dimethyl sulphoxide paper chromatography.

The N.M.R. spectrum of the reaction product in deutero-chloroform was identical to the spectrum of the product obtained using anhydrous acetic acid as solvent. Once more, only a weak signal was observed at τ 5.40 indicating that there was little, if any, glycollic ester in the reaction product.

Anhydrous Methanol.

Criegee⁶⁹ has suggested that the solvolysis of lead tetraacetate in alcohols proceeds by the general equation (viii), to give an unstable intermediate of the type, $ROPb(OAc)_3$. This intermediate is decomposed rapidly in moist solvent to give lead dioxide, but in anhydrous alcohol the decomposition is thought to proceed by equation (ix) to give alkoxide cation.



This interesting suggestion led us to investigate the reaction of D-glucal triacetate with lead tetraacetate in anhydrous methanol. It was hoped that this reaction would

provide a convenient route for the preparation of 2-O-methyl sugars obtained by electrophilic attack on the double bond of methoxyl cation produced by equation (ix).

Since the intermediate, $\text{MeOPb}(\text{OAc})_3$, is very unstable in daylight, the glycal was treated with lead tetraacetate in anhydrous methanol at room temperature in the dark. A large excess of lead tetraacetate was necessary because a considerable amount of the lead salt decomposed with oxidation of the solvent to formaldehyde. Paper chromatography, using dimethyl sulphoxide as stationary phase, on the dextrorotatory syrup obtained after removal of inorganic salts, showed the presence of a fast moving product, together with small amounts of unchanged glycal and several materials which remained near the starting line. These slow moving materials were shown to be partially acetylated derivatives of methyl α -D-mannopyranoside because they gave this glycoside on deacetylation, and its tetraacetate on acetylation.

If the reaction had involved the introduction of methoxyl at $\text{C}_{(2)}$, then 2-O-methyl-D-glucose, 2-O-methyl-D-mannose, or their glycosides would be obtained on deacetylation. However, the deacetylated reaction product was shown by paper chromatography to contain no 2-O-methylated glucose or mannose. In addition, acid hydrolysis of this deacetylated product failed to give these methylated sugars, only D-mannose being produced. It would appear, therefore, from these results that the reaction of the glycal with lead tetraacetate in methanol

has not involved electrophilic attack by methoxyl cation on the double bond.

For a considerable time we were unable to establish the exact nature of the reaction occurring under the above conditions. A first clue was provided by N.M.R. spectroscopy which indicated that orthoacetate formation was involved.

N.M.R. spectroscopy is well suited to the characterisation of orthoacetates because the chemical shift for the C-methyl protons in these compounds is at a higher field than that of protons encountered in other types of carbohydrate structures. Thus, examination of the spectrum of the reaction product in deuteriochloroform showed the presence of two peaks in ratio 3 : 1 at τ 8.35 and 8.49 respectively. These signals appeared in the same ratio at τ 8.38 and 8.45 in the spectrum of the deacetylated product in deuterium oxide. These values, which agree closely with those found by Perlin⁷⁹ for the C-methyl protons of mannose 1,2-orthoacetates, probably correspond to the two stereochemical forms of one orthoacetate.

Convincing evidence for the presence of diastereoisomeric orthoacetates was provided by the treatment of the deacetylated product in deuterium oxide with a trace of acid. This treatment resulted in the rapid disappearance of the C-methyl signals and their replacement by a single peak at τ 7.88 attributable to a single acetoxyl group. This decomposition, which also occurred more slowly in deuterium oxide alone, was strongly retarded by the addition of base to the solution.

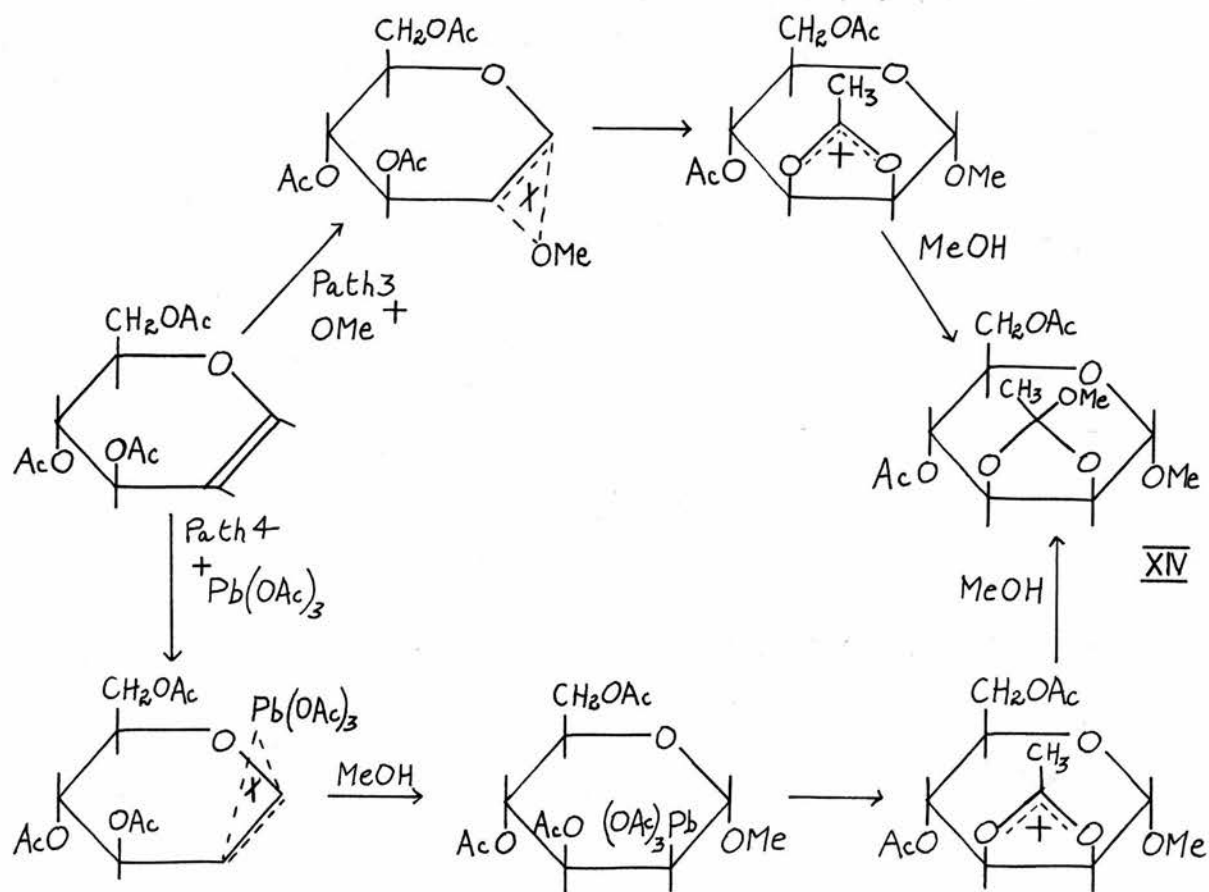
Examination of the hydrolysate by paper chromatography showed the disappearance of the fast moving orthoacetate spot, and the appearance of a slower moving material which was thought to be a monoacetate of methyl α -D-mannopyranoside. This was confirmed by its conversion to this glycoside on deacetylation.

Since the only adjacent cis hydroxyl groups in methyl α -D-mannopyranoside are attached to C₍₂₎ and C₍₃₎, this suggests that the main product formed on treatment of D-glucal triacetate with lead tetraacetate in methanol is methyl α -D-mannopyranoside diacetate 2,3-(methyl orthoacetate) (XIV). This was confirmed by examination of the material obtained by methylation of the deacetylated reaction product using the procedure of Kuhn and Trischmann.⁸⁰ The N.M.R. spectrum of the methylated product indicated the replacement of the orthoacetate C-methyl signal by that of acetate. Gas-liquid chromatography on the syrup obtained on deacetylation showed the presence of penta-O-methyl-D-mannose together with a substituent with identical retention times on two column packings to an authentic specimen of methyl 4,6-di-O-methyl- α -D-mannopyranoside. Since only traces of other partially methylated sugars were present, this indicates that the opening of the orthoacetate ring had occurred after methylation during the working up. The formation of the 4,6-dimethyl-D-mannoside indicates that the orthoacetate group in the original reaction product was attached to C₍₂₎ and C₍₃₎.

The question now arises as to how the 2,3-orthoacetate (XIV)

was formed in the reaction. It seems unlikely that the reaction has involved migration of the double bond of the glycal to the 2,3-position, followed by attack of acetate cation from lead tetraacetate. A more likely pathway to the 2,3-orthoacetate would appear to be the formation of an acetoxonium ion intermediate by participation of the 3-acetoxyl group of the glycal in the displacement of a group attached to C₍₂₎. Neutralisation of the acetoxonium ion by solvent would give the methyl orthoacetate.

Two possible routes to the orthoacetate, involving participation of the acetoxyl group on C₍₃₎ of the glycal, are shown below:



Path 3 involves an initial electrophilic attack by methoxyl cation on the double bond of the glycal to give a "methoxonium ion", which is opened by trans attack of the 3-acetoxyl group to give the desired acetoxonium ion intermediate. There seems to be no precedent for such a mechanism, although methoxonium ions have been postulated as intermediates in certain neighbouring group reactions.⁸¹ Path 4 involves initial addition of OMe and Pb(OAc)₃ by a reaction analagous to methoxymercuration, followed by breaking of the C—Pb bond with simultaneous or subsequent attack by the neighbouring acetoxyl group. An obvious criticism of this second mechanism is that it postulates a cis neighbouring group displacement. This difficulty could be avoided by postulating cis addition^{31,32} to the glycal to give a methoxylead compound with the α -D-gluco-configuration which then undergoes a normal trans displacement. (A mechanism of this type might also be invoked for the reaction in acetic acid discussed earlier.) The formation of a methoxylead compound with the β -D-gluco-configuration might have been expected from the results of the methoxymercuration of D-glucal triacetate; this would have given an orthoacetate of methyl β -D-mannopyranoside and it is interesting that methyl β -D-mannopyranoside could not be detected in the material obtained after removal of the orthoacetate group from the deacetylated product.

It seems impossible to decide between these two mechanisms in the absence of further evidence.

Although the presence of two orthoacetates has been established from the N.M.R. spectrum of the reaction product, no separation of these orthoacetates could be effected by paper chromatography. A similar failure was experienced in the attempted separation of the orthoacetates in the deacetylated product by paper electrophoresis in 0.5N-sodium hydroxide. However, this latter method did suggest that the difference in acidity between the orthoacetates, and the D-glucal and methyl α -D-mannopyranoside also present in the product, was sufficient to warrant a separation on a column of ion-exchange resin in the hydroxide form.⁸² By this means it was hoped to isolate the orthoacetates uncontaminated with the other materials. It was found, however, that although the orthoacetates could be conveniently freed from methyl α -D-mannopyranoside on such a column, the orthoacetate fraction was contaminated with a small amount of D-glucal. By careful evaporation of this fraction in the presence of dilute ammonium hydroxide to prevent decomposition of the orthoacetate, a syrupy orthoacetate mixture could be obtained. We were unable to isolate a crystalline material from this mixture because of the tendency of the orthoacetates to decompose into the monoacetate. This lability prevented other methods of purification such as distillation from being employed.

It was not possible, due to the lack of time at our disposal, to investigate further this interesting reaction between D-glucal triacetate and lead tetraacetate in methanol.

The results thus far obtained have provided convincing proof that the product of the reaction consists of the diastereoisomeric forms of methyl α -D-mannopyranoside diacetate 2,3-(methyl orthoacetate) (XIV). It is indeed unfortunate that a pure orthoacetate could not be isolated because few orthoacetates described in the literature have the orthoacetate grouping attached to positions other than C₍₁₎ and C₍₂₎ of the sugar ring. Reese and Sulston⁸³ have recently reported what would appear to be a general method for the formation of an orthoacetate grouping on any adjacent cis hydroxyl groups in a pyranose or furanose ring and it would be of interest to attempt the synthesis of the above orthoacetate by this method.

EXPERIMENTAL

For experimental procedures not discussed below see General Information in Part I.

Acetic acid and benzene solvents were of A.R. quality. Anhydrous acetic acid was prepared by distillation from boron triacetate⁷⁶ according to the procedure of Eichelberger and LaMer.⁷⁷ Benzene was dried over sodium wire, then distilled from sodium.

Lead tetraacetate (B.D.H. Ltd.) was obtained as a slurry in acetic acid. The reagent was freed from acetic acid prior to use by blotting between filter paper, then drying overnight over phosphorus pentoxide/potassium hydroxide in vacuo.

The amount of lead tetraacetate remaining in the reaction solution was determined at intervals using the procedure of Goldschmid and Perlin.⁸⁴ This involved the addition of a suitable volume of the reaction solution to a freshly prepared aqueous solution of sodium acetate, potassium iodide and acetic acid, and the estimation of the liberated iodine by titration against standard sodium thiosulphate solution using starch indicator.

The excess of lead tetraacetate remaining at the end of the reaction was destroyed by the addition of an excess of ethylene glycol to the reaction solution.

After removal of solvents by evaporation, the carbohydrate material was freed from lead salts by dissolution in chloroform,

and thorough washing of the organic layer with water and aqueous sodium bicarbonate solution. Evaporation of the dried organic layer gave the reaction product.

(1) The Reaction of Sugar Methoxymercurials with Lead Tetraacetate in Acetic Acid.

(i) Methyl 2-chloromercuri-2-deoxy- α -D-mannopyranoside triacetate.¹¹

The mercurial (0.27 g., 0.50 mmoles) was heated at 60° with lead tetraacetate (0.32 g., 0.71 mmoles) in acetic acid (20 ml.). The optical rotation of the solution rose to a steady value (α in 1 dm. tube +0.30°) in ca. 2 hours, and estimation of the lead tetraacetate remaining in the solution indicated that 1 mole had been consumed. A syrupy product (0.16 g.), OMe = 1.60%, was obtained after removal of acetic acid and lead salts. If the reaction had involved the replacement of HgCl by OAc, then a methoxyl content of 8.55% would have been expected. The reaction product remained on the starting line on paper chromatography using solvent (vi), spray (a), and there was no indication of any methyl α -D-mannopyranoside or glucopyranoside tetraacetates being present (both, R_F ca. 0.61). Paper chromatography in solvent (vii), spray (a), showed the presence of a material (R_F ca. 0.30) together with small amounts of other constituents at R_F ca. 0.19 and ca. 0.13. Chromatography in these solvent systems using spray (c) indicated that the mercurial had been completely decomposed to give products which did not contain mercury.

Deacetylation gave a product which was shown by paper chromatography with solvents (iii) and (iv), spray (b), to consist of D-mannose with a trace of D-glucose.

Acetylation of the reaction product (0.13 g.) with acetic anhydride in pyridine gave a syrupy pentaacetate mixture (0.13 g.), which on crystallisation from aqueous methanol gave α -D-mannose pentaacetate (0.10 g.), m.p. 73° , $[\alpha]_D +54^{\circ}$ (c 1 in CHCl_3). The mixed m.p. with an authentic specimen gave no depression. The mother liquor was shown by paper chromatography, in solvent (vi), spray (a), to contain the pentaacetates of α -D-mannose (R_F ca. 0.47), β -D-mannose (R_F ca. 0.27) and β -D-glucose (R_F ca. 0.37).

(ii) Methyl 2-acetoxymercuri-2-deoxy- β -D-glucopyranoside triacetate.¹⁰

The procedure and quantities were those described above for the reaction of the α -D-manno-mercurial with lead tetraacetate in acetic acid, except that longer heating was required to complete this reaction (ca. 4 hours at 60°). Paper chromatography on the reaction product suggested that it was identical to that obtained from the α -D-manno-mercurial above. This was confirmed by deacetylation which gave only D-mannose and a trace of D-glucose, while acetylation gave their pentaacetates.

(2) The Reaction of Methoxymercurials with Nitrosyl Chloride.

The mercurials used in the reactions with nitrosyl chloride were methyl 2-chloromercuri-2-deoxy- α -D-talopyranoside

triacetate and cyclohexyl α -methoxymercurichloride.¹²

The nitrosyl chloride reagent was prepared by the following methods:

(i) the reagent was prepared in situ by the addition of the requisite amount of anhydrous hydrogen chloride in alcohol-free chloroform to a solution of n-butyl nitrite in the same solvent.

(ii) the reagent was used as a solution of the gas in either dioxan or dichloromethane. Gaseous nitrosyl chloride was prepared by the passage of dinitrogen tetroxide over moist potassium chloride.⁸⁵ After drying, the nitrosyl chloride was bubbled through the solvent until a solution of the desired strength was obtained.

Methyl 2-chloromercuri-2-deoxy- α -D-talopyranoside triacetate was reacted with nitrosyl chloride under the following conditions:

(a) a solution of the mercurial and n-butyl nitrite in chloroform at 0° was treated with a solution of anhydrous hydrogen chloride in the same solvent.

(b) the mercurial dissolved in dioxan was treated at room temperature with a solution of nitrosyl chloride in the same solvent.

These reactions appeared to be very rapid because mixing of the reagents resulted in an almost immediate deposition of mercuric chloride. In each case the mercury-free products gave negative Lassaigne tests for nitrogen which suggests

that deoxymercuration had occurred. This was confirmed by the examination of the products obtained from the reaction of cyclohexyl α -methoxymercurichloride with nitrosyl chloride under conditions (a) and (b) above, and also with a solution of the gas in dichloromethane at -25° . Gas-liquid chromatography showed that cyclohexene was the chief constituent in the products from these reactions.

(3) The Reaction of $\underline{\underline{D}}$ -Glucal Triacetate with Lead Tetraacetate in Various Solvents.

(i) Acetic Acid.

In a preliminary experiment to discover the stability of $\underline{\underline{D}}$ -glucal triacetate in acetic acid, a 1.5% glycal solution was allowed to stand at room temperature for 1 week, then was heated at 60° for 4 hours. The optical rotation of this solution was unaffected by this treatment which indicated that no decomposition had occurred. This was confirmed by the recovery of the glycal in 80% yield from the reaction solution; paper chromatography on the mother liquor indicated the absence of decomposition products.

The reaction of $\underline{\underline{D}}$ -glucal triacetate (0.816 g., 3.00 mmoles) with lead tetraacetate (1.710 g., 3.85 mmoles) in acetic acid (80 ml.) at room temperature was accompanied by a slow rise in the optical rotation (α in 2 dm. tube $-0.20^{\circ} \rightarrow +0.80^{\circ}$, steady value, in 4 days), one mole of lead salt being consumed. Removal of inorganic salts gave a syrupy product (0.92 g.) which remained on the starting line on paper chromatography

using solvent (vi), spray (a). There was no suggestion of faster moving pentaacetates being present in the reaction product (i.e. pentaacetates of α -D-mannose, R_F ca. 0.47; β -D-mannose, R_F ca. 0.27; α -D-glucose, R_F ca. 0.56 and β -D-glucose, R_F ca. 0.37). Chromatography in solvent (vii), spray (a), showed the presence of a material at R_F ca. 0.30 with small amounts of other products at R_F ca. 0.19 and ca. 0.13.

The deacetylated product was shown by paper chromatography, solvents (iii) and (iv), to consist of D-mannose and a trace of D-glucose.

Acetylation of the reaction product gave a syrupy mixture (0.82 g.) which gave α -D-mannose pentaacetate (0.70 g., 60%), m.p. 73° , $[\alpha]_D +53^\circ$ (CHCl_3), on crystallisation from aqueous methanol. The mixed m.p. with an authentic specimen gave no depression. The mother liquor was shown by chromatography in solvent (vi) to contain the pentaacetates of α - and β -D-mannose and β -D-glucose.

(ii) Anhydrous Acetic Acid.

D-Glucal triacetate (0.70 g., 2.57 mmoles) was shaken for 12 hours with a slurry of lead tetraacetate (3.45 g., 7.78 mmoles) in anhydrous acetic acid (10 ml.). Estimation of the tetravalent lead remaining in the reaction mixture indicated that approximately 2 moles of lead tetraacetate had been consumed. The dextrorotatory syrup (0.82 g.) obtained after freeing from inorganic salts was shown by paper

chromatography in solvent (vi), spray (a), to consist of numerous materials which appeared on or near the starting line. The pattern of spots was not appreciably altered by acetylation. There was no suggestion of any faster moving pentaacetates being present in either the original or acetylated products.

Paper chromatography on the deacetylated product in solvents (iii) and (iv), spray (b), showed the presence of D-mannose and small amounts of D-glucose and a faster moving material which might be 2-deoxy-D-glucose. The presence of D-mannose in the deacetylated product was confirmed by the preparation of its phenylhydrazone, m.p. 199° (decomp.).⁸⁶ Mixed m.p. with an authentic specimen caused no depression.

When the above reaction was repeated using equimolar quantities of glycal and lead salt, again no pentaacetates were produced. The product was shown by paper chromatography to consist of the slow moving materials obtained above, together with an appreciable amount of unchanged glycal.

Two moles of lead tetraacetate were consumed in the reaction of the lead salt with D-glucal triacetate in anhydrous acetic acid containing ca. 10% sodium acetate. Although paper chromatography suggested the presence of pentaacetates in the product, the chief constituents were the slow moving products obtained above.

(iii) Anhydrous Benzene.

D-Glucal triacetate (0.65 g., 2.39 mmoles) was heated at 60° with a suspension of lead tetraacetate (3.20 g., 7.23 mmoles)

in benzene (10 ml.). Paper chromatography in solvent (vi) on this solution at intervals indicated that all the glycal had reacted after 8 hours. Estimation of the lead tetraacetate remaining in the solution indicated that ca. 2 moles had been consumed. The dextrorotatory product (0.76 g.) was chromatographically identical to the product obtained using anhydrous acetic acid as solvent. Acetylation of the reaction product did not change the pattern of spots, while deacetylation gave D-mannose (isolated as the phenylhydrazone, m.p. and mixed m.p. 199°) and small amounts of D-glucose and a faster moving material with identical chromatographic properties to 2-deoxy-D-glucose.

The product obtained on repeating the above reaction with equimolar amounts of each reactant was shown by paper chromatography to consist of the slow moving products as before, together with unchanged glycal.

(iv) Anhydrous Methanol.

D-Glucal triacetate (2.00 g., 7.35 mmoles) was shaken with lead tetraacetate (9.12 g., 20.56 mmoles) in anhydrous methanol (60 ml.) in the dark for 12 hours. It was found that the initial yellow colour of the reaction solution was discharged after this time to give a colourless solution which smelt strongly of acetic acid and formaldehyde. This solution was repeatedly evaporated to half bulk with chloroform (60 ml.) in an attempt to remove the acetic acid by distillation prior to concentration. Removal of lead salts gave a

colourless syrup (1.90 g.), $[\alpha]_D$ ca. $+30^\circ$ (MeOH), which was shown by paper chromatography in solvent (vi), spray (a), to consist of a fast moving product (R_F ca. 0.80) together with small amounts of unchanged glycal (R_F ca. 0.65) and several slow moving materials (R_F ca. 0.08 and ca. 0.15). The latter were shown to be partially acetylated derivatives of methyl α -D-mannopyranoside because they were converted to methyl α -D-mannopyranoside tetraacetate (R_F ca. 0.60, solvent vi) on acetylation.

The N.M.R. spectrum of the reaction product in deuteriochloroform showed the presence of two C-methyl signals in a ratio of about 3 : 1 at τ 8.35 and 8.49 indicating the presence of two orthoacetates.

Deacetylation of the reaction product gave a non-crystallisable syrup (A), which was shown by paper chromatography in solvent (i), spray (b), to consist of a fast moving material (R_F 0.77), together with small amounts of D-glucal (R_F 0.53) and methyl α -D-mannopyranoside (R_F 0.34). The latter compound could be conveniently isolated in the crystalline form, m.p. and mixed m.p. $192-194^\circ$, by crystallisation of the deacetylated product (A) from hot ethanol. The product (A) did not contain any 2-O-methyl-D-glucose (R_F 0.24, solvent i) or 2-O-methyl-D-mannose (R_F 0.28, solvent i). Acid hydrolysis⁸⁷ of a little of the deacetylated product by heating with 0.5N-hydrochloric acid at 100° for 4 hours failed to give these methylated sugars, the chief product appearing to be

D-mannose (R_F 0.11, solvent i).

The N.M.R. spectrum of the deacetylated product (A) in deuterium oxide showed the presence of two orthoacetate C-methyl signals in a ratio of about 3 : 1 at τ 8.38 and 8.45. This solution decomposed slowly as was shown by the disappearance of the orthoacetate signals and the appearance of an acetate signal at τ 7.88. This decomposition occurred within 5 minutes of dissolution of product (A) in 0.01M-hydrochloric acid. However, the orthoacetates were found to be stable for several days at room temperature in dilute ammonium hydroxide solution. Paper chromatography, solvent (i), spray (b), on the decomposition solution showed that the fast moving orthoacetate material (R_F 0.77) had been replaced by the monoacetate at R_F 0.60. Paper chromatography in solvent (i) on the decomposition solution after deacetylation with sodium methoxide in methanol showed the disappearance of the monoacetate of methyl α -D-mannopyranoside (R_F 0.60) and the increase in intensity of the free glycoside spot (R_F 0.34).

A little of the deacetylated reaction product was methylated with dimethyl sulphate in dimethyl formamide/dimethyl sulfoxide in the presence of barium hydroxide octahydrate.⁸⁰ The N.M.R. spectrum of the methylated product in deuteriochloroform showed the disappearance of the orthoacetate C-methyl signals and their replacement by an acetate signal at τ 7.85. Gas-liquid chromatography on this methylated material after deacetylation showed the presence of

penta-O-methyl- α -D-mannose together with a constituent with identical retention times on butan-1,4-diol succinate and polyphenyl ether column packings to an authentic specimen of methyl 4,6-di-O-methyl- α -D-mannopyranoside.⁸⁸

Chromatographic separation of the constituents in product (A) was attempted on a freshly prepared column of Dowex 1X2 ion-exchange resin (200-400 mesh) in the hydroxide form. Water was used as eluting solvent and the fractions collected were made mildly alkaline with ammonium hydroxide. If this latter precaution was not observed, decomposition of the orthoacetate to the monoacetate occurred readily on concentration of the fractions. Evaporation of the eluate in the presence of ammonium hydroxide gave methyl α -D-mannopyranoside, m.p. and mixed m.p. 192-193⁰, in the first fractions and a syrupy orthoacetate mixture in later fractions. The latter was shown by paper chromatography in solvent (i), spray (b), to consist of the 2,3-orthoacetate (R_F 0.77) together with D-glucal (R_F 0.53). Attempts to isolate a crystalline orthoacetate by crystallisation of this fraction from several solvents failed because of the tendency of the orthoacetate to decompose to the monoacetate.

PART III

A. An Investigation of the Reaction of D-Glucal Triacetate
with Some Mercurials.

It has been reported in Part I of this thesis that the methoxymercuration of glycals with mercuric acetate in methanol proceeds rapidly to completion. In general, it has been found that the optical rotation of the methoxymercuration solution reaches a steady value within 20 minutes, which does not change on allowing the solution to stand at room temperature for several weeks. This result illustrates the stability of the glycal adducts in the reaction solutions.

A different result to the above has already been noted in the competition reaction between D-glucal and D-galactal triacetates for mercuric acetate (Part I). Although the optical rotation of the solution appeared to reach a steady value within 20 minutes of mixing of the reagents, a slow reaction occurred over several weeks as was shown by the upward drift of the optical rotation of the solution. Since this competition experiment differs from normal methoxymercuration reactions by the presence of unchanged glycals in the final solution, these glycals might be expected to be the cause of the slow reaction. This was confirmed by the observation of a similar drift in the rotation on the addition of D-glucal triacetate to the optically stable solution obtained from the

reaction of equimolar quantities of this glycal and mercuric acetate in methanol.

The slow reaction occurring on the addition of a glycal to a sugar mercuriacetate appears to be general, because it has been observed with a variety of glycals and sugar mercurials. However, although the unchanged glycals in the solution have been shown to be the source of the drift in rotation, it remained to establish the exact nature of the reaction causing this rotation change. Further investigation into this phenomenon indicated that several reactions were involved; these were examined and partially elucidated and this work will now be considered.

It was originally thought that these slow reactions might involve nothing more complicated than a reaction of the unchanged glycals catalysed by the acetic acid produced in the methoxymercuration. This possibility could be eliminated, however, because glycals were found to be stable in methanolic acetic acid under the appropriate conditions.

Dimethyl sulphoxide paper chromatography⁵⁶ provided a first clue as to the nature of one of the reactions occurring under these conditions. The addition of D-galactal triacetate to the methoxymercuration product of D-glucal triacetate resulted in a slow rise in rotation over 4 weeks; paper chromatography on the reaction solution after the addition of sodium chloride to convert the mercurials to the mercurichlorides, showed the presence of the expected α -D-manno-mercurial

(I; R = Ac, X = Cl) and the β -D-gluco-isomer (II; R = Ac, X = Cl) together with an appreciable amount of the α -D-talo-mercurichloride (IX; R = Ac, X = Cl). The appearance of the latter is unexpected and suggests that a "transmercuration reaction" has occurred involving the transference of the mercury group from one sugar residue to the other.

Transmercuration appears to be a general reaction under these conditions because paper chromatography on the product from the addition of D-glucal triacetate to the D-galactal triacetate mercuration solution showed the presence of the β -D-gluco- and α -D-manno-isomers, together with the expected α -D-talo-compound. Furthermore, the relative intensities of these materials on paper chromatography suggested that the mercurials were present in the same proportions as those produced from the addition of D-galactal triacetate to the D-glucal triacetate mercuration solution. This result would suggest that an equilibrium between the various mercurials is set up in these reactions.

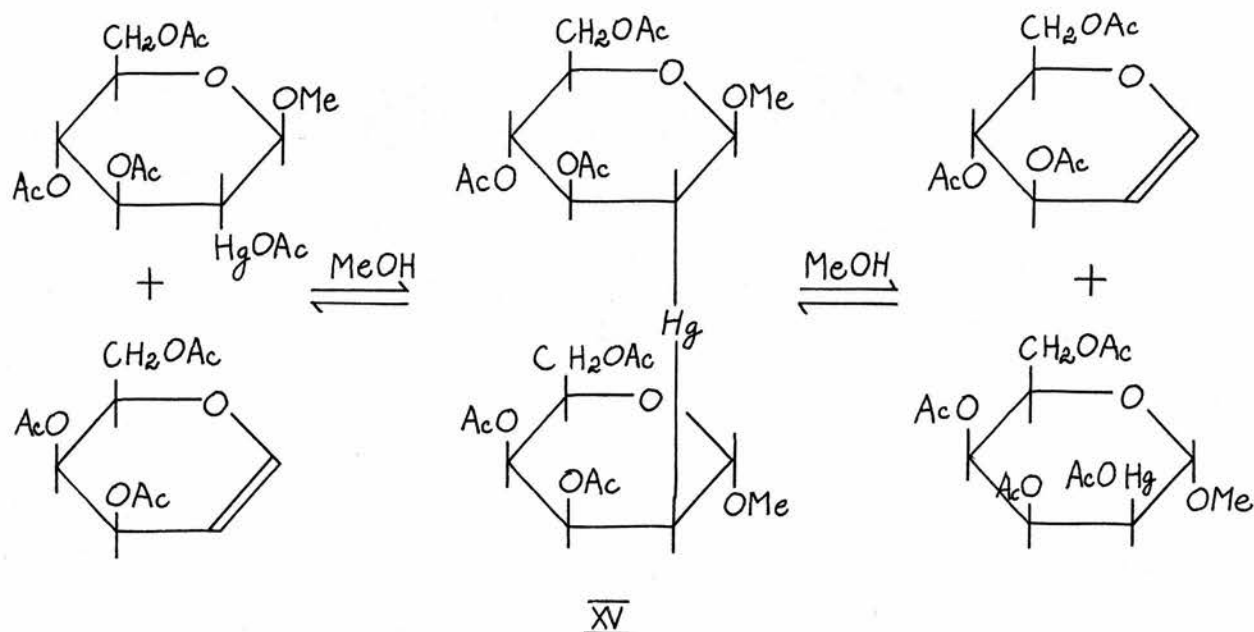
A transmercuration equilibrium similar to the above has also been observed on the addition of D-glucal triacetate to methyl 2-acetoxymercuri-2-deoxy- β -D-glucopyranoside triacetate¹⁰ in methanol; paper chromatography on the reaction product after addition of sodium chloride showed that the α -D-manno-isomer (I; R = Ac, X = Cl) was the chief mercury-containing constituent, together with only a trace of the β -D-gluco-isomer (II; R = Ac, X = Cl). Since this equilibrium was not

attained in the absence of excess glycal (although a slow deacetylation occurred), this indicates that the glycal is necessary to provide a pathway for the equilibration of the mercurials in the transmercuration reactions.

It would be advantageous to confirm that transmercuration was involved in the above reactions by isolation of the mercurials produced by mercury exchange. This would be difficult in the systems described above, however, because the mercurials are insufficiently separated by paper, thin-layer and ion-exchange paper chromatography (Part I). Thus, the simpler system of methyl 2-acetoxymercuri-2-deoxy- α -D-mannopyranoside (I; R = H, X = OAc) with cyclohexene in methanol was studied in the hope that the mercurials produced by transmercuration could be isolated. A slow reaction was observed in this system and paper and thin-layer chromatography on the product, after conversion to the mercurichloride, indicated that three mercurials were present with R_F values corresponding to the expected α -D-manno-mercurial (I; R = H, X = Cl), the β -D-gluco-mercurial (II; R = H, X = Cl)¹⁰ and cyclohexyl α -methoxymercurichloride.¹² The chromatographic assignments to the latter two compounds were confirmed by the isolation of these mercurials in the crystalline form. This result establishes, therefore, that transmercuration is one of the reactions occurring in the above systems.

Since the presence of excess glycal or other cycloolefin in the solution with the mercuriacetate is necessary for

transmercuration to proceed, it seems likely that transmercuration involves some sort of reaction between the sugar mercuri-acetate and the unsaturated material. It is easy to visualise transmercuration if a mechanism involving a bis mercury intermediate is proposed. Thus, the formation of the α -D-talo-mercurial from the reaction of D-galactal triacetate with the β -D-gluco-mercuriacetate from D-glucal triacetate, is shown below:



Although no bis mercury compounds of the type (XV) have been detected, let alone isolated, in these reactions, this does not invalidate the above mechanism. Wright and his co-workers^{12,14} have proposed a bis mercury intermediate similar to the above in the free radical epimerisation of the C—Hg bond in oxymercurial adducts of cycloolefins. Bis mercury compounds have also been postulated as intermediates in the transvinylation equilibria reported by Watanabe and Conlon⁸⁹

(see later). In general, these intermediates have been found to be very unstable and difficult to isolate.

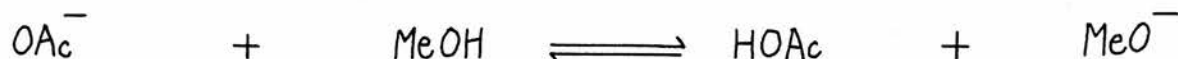
In addition to the transmercuration reaction which occurs on the addition of a glycol to a sugar mercuriacetate, another slow reaction has been discovered which involves a modification of the glycol by the mercuriacetate group. This modification was studied initially on the reaction of the acetylated β -D-gluco-mercuriacetate (II; R = Ac, X = OAc) with D-glucal triacetate in methanol. The modification appeared to be general, however, because it was found that the mercury-free products from this reaction were identical to those obtained using phenyl mercuriacetate in place of the sugar mercurial. Since the β -D-gluco-mercuriacetate was found to undergo a slow deacetylation in methanol (Part III, B), it was decided to study this glycol modification using the simpler system of phenyl mercuriacetate and D-glucal triacetate in methanol.

The reaction of D-glucal triacetate with phenyl mercuriacetate in methanol was accompanied by a slow rise in rotation, 1 mole of acetic acid being produced. Paper and thin-layer chromatography on the product (A) from this reaction indicated that the glycol had almost completely reacted to give two mercury-free products. Although subsequent work (Table I; Part III, B) showed that phenyl mercuriacetate could act as a weak deacetylating agent in methanol, the absence of slow moving constituents in dimethyl sulphoxide paper chromatography

on product (A) suggested that little deacetylation had occurred in this reaction. The deacetylating action of the mercurial has probably been suppressed by the acetic acid produced in this reaction. An interesting feature of the N.M.R. spectrum of product (A) was the presence of two sharp signals in a ratio of about 1 : 2 at τ 6.52 and 6.69 respectively. Since the chemical shifts of these signals are similar to those found for glycoside methoxyls, it was thought that glycoside formation might be involved in the modification of the glycal.

Before proceeding further with our examination of the reaction product, it was necessary to find a convenient means of removing the mercury salt from the carbohydrate material. Paper chromatography on a variety of Amberlite ion-exchange papers was performed to ascertain whether ion-exchange could be used to effect this separation. It was found that the carbohydrate product could be separated from the mercurial by chromatography on Amberlite WA-2 paper in the sodium form, using methanol as eluant. Since this paper incorporates Amberlite IRC-50 (Na^+) ion-exchange resin, then it might be expected that a column separation on this resin would be equally effective. This was found to be the case, a syrupy mercury-free material (B) being obtained from the eluate on passage of product (A) down a column of the resin. Unfortunately, however, product (B) was contaminated with sodium acetate which had been produced on the column by the exchange of mercury for sodium.

The chromatographic properties of product (B) were found to differ from those of the original material (A), indicating that a change had occurred on the column. This change was found to involve deacetylation of product (A), catalysed by methoxide ion which was produced by the equilibrium between sodium acetate and the solvent:



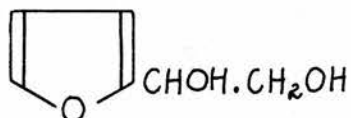
This interesting observation led us to investigate the kinetics of deacetylations with sodium acetate in methanol and this work is discussed in Part III, B.

The deacetylated product (B), which gave negative reactions with ferric chloride and Fehling's solutions, was shown by paper chromatography, using a developing spray which was sensitive to unsaturated compounds (alkaline permanganate solution), to consist of two unsaturated products together with a trace of D-glucal. The U.V. spectrum of this product showed the presence of a peak $< 190 \text{ m}\mu$ (maximum not reached) which probably corresponds to the ethylenic chromophore.

Acetylation of product (B) gave a syrupy product (C) with chromatographic properties which differed from those of the expected product (A). Since (C) could also be obtained by acetylation of (A), this suggests that the latter contains partially acetylated sugar derivatives. Deacetylation of products (A) and (C) with sodium methoxide in methanol gave the deacetylated product (B) and this indicates that decomposition

or rearrangement have not occurred on acetylation or deacetylation.

The decompositions which were observed on the addition of a trace of acid to the deacetylated and acetylated reaction products (B) and (C), provided some insight into the nature of these products. Thus, it was found that the addition of acid to the deacetylated product in water resulted in the immediate appearance of a peak at $\lambda_{220} \text{ m}\mu$, $\epsilon_{\text{max.}} 5000$, in the ultraviolet at the expense of the maximum at lower wavelength mentioned earlier. The N.M.R. spectrum of the decomposition solution indicated the disappearance of the "glycoside peaks" at $\tau 6.57$ and 6.67 . The spectrum was comparatively simple and was analysed as being consistent with the monosubstituted furan,



, which is probably the

source of the peak in the ultraviolet, e.g. furfuryl alcohol, $\lambda_{\text{max.}} 217 \text{ m}\mu$, $\epsilon_{\text{max.}} 8000$. The assignment to the furan was confirmed by showing that furfuraldehyde was produced on periodate oxidation of this decomposition solution.

Although the N.M.R. intensities suggested the presence of another material in the decomposition solution above in a similar amount to the furan, this material could not be identified.

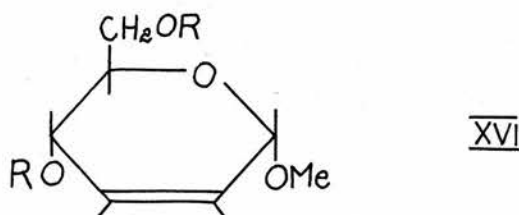
The addition of a trace of acid to the acetylated product (C) in aqueous ethanol resulted in the immediate appearance of a peak, $\lambda_{\text{max.}} 210 \text{ m}\mu$, in the ultraviolet. The N.M.R.

spectrum of this decomposition solution which bore little resemblance to that of the product (C), showed an interesting pattern of peaks at low field. Examination of the chemical shifts and coupling constants of the latter suggested that a trans 2,3-unsaturated aldehyde had been formed in the decomposition. This aldehyde is probably the source of the maximum in the ultraviolet since trans crotonaldehyde has a maximum at λ 220 $m\mu$ in the ultraviolet. Calculation of the N.M.R. intensities indicated that this aldehyde constituted approximately one third of the decomposition material; the remainder of the product could not be identified.

Although the results described above suggest that unsaturated compounds are produced on treatment of D-glucal triacetate in methanol with phenyl mercuriacetate, it remained to establish the position of the double bond in these products. This was done by examination of the products obtained on treatment of syrup (C) with potassium permanganate in aqueous acetone, a reagent which gives cis diols from an olefin.⁹⁰ Methyl α -D-mannopyranoside was isolated in the crystalline form from the oxidation product after deacetylation and this was taken to suggest the presence of a 2,3-unsaturated glycoside in the original material. Acid hydrolysis of the oxidised material gave a syrupy mixture which was shown by paper chromatography in neutral, basic, acidic and borate solvents to consist of glucose, mannose and altrose. The presence of altrose in the oxidation product was taken initially as evidence

for the production of a 3,4-unsaturated glycoside.

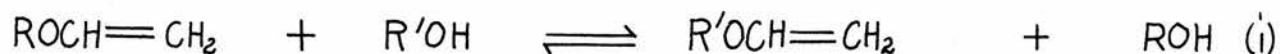
It was considered initially that the experimental results were consistent with a 2,3-unsaturated glycoside of structure (XVI) having been produced in the reaction of D-glucal triacetate and phenyl mercuriacetate in methanol. Thus, this structure is compatible with the formation of the 2,3-unsaturated aldehyde and the monosubstituted furan which are produced on the addition of acid to the acetylated and deacetylated products respectively. Furthermore, the isolation of methyl α -D-mannopyranoside from the oxidised material appeared to confirm the presence of a 2,3-unsaturated glycoside in the original product.



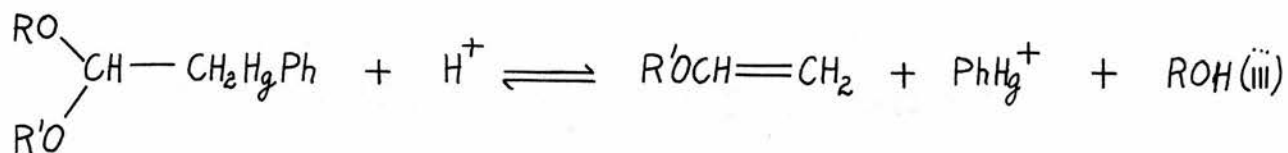
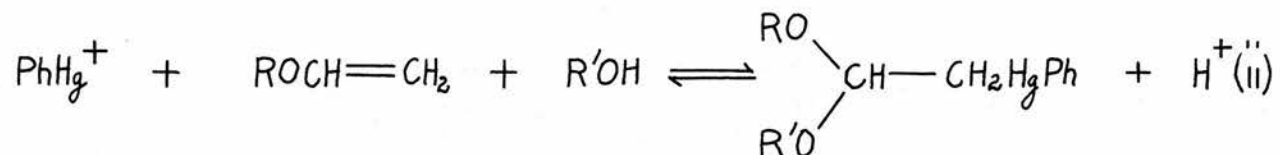
Dr. R. J. Ferrier has kindly supplied us with an authentic specimen of the above compound (XVI; $R = \text{Ac}$), in a mixture with the β -glycoside. Although the N.M.R. spectrum of this mixture bore a resemblance to that of the acetylated product (C), the chromatographic properties of these materials were completely different. This indicates that the 2,3-unsaturated glycoside (XVI) cannot be one of the constituents in the reaction product.

An alternative interpretation of the experimental results was suggested by Ferrier⁹¹ and this will now be considered.

Watanabe and Conlon⁸⁹ have reported that mercuric salts of weak acids, including phenyl mercuriacetate, are effective in catalysing the transfer of vinyl ethers to alcohols (equn. i).

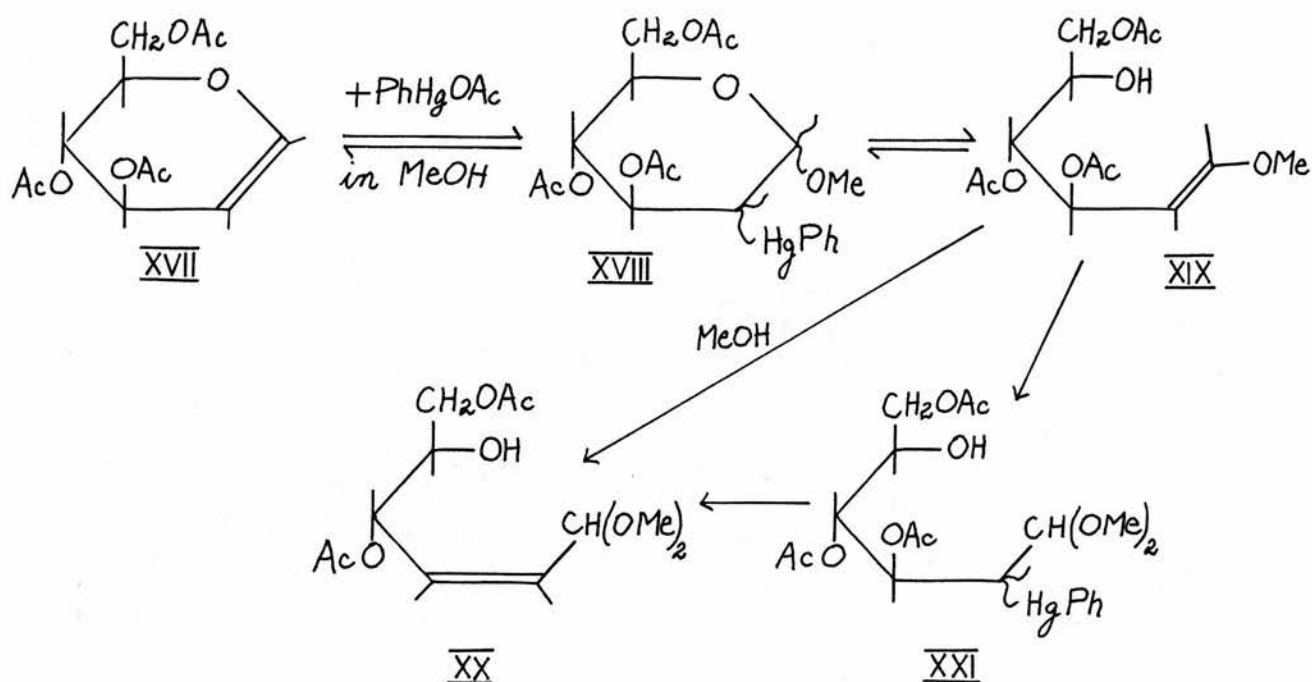


These workers propose that this reversible transvinylation equilibrium proceeds through the intermediate steps, (ii) and (iii), which are shown below with phenyl mercuriacetate as catalyst.

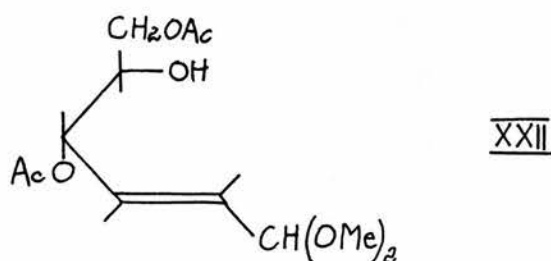


Since D-glucal triacetate may be regarded as a vinyl ether, then it would not be surprising if a similar transvinylation to the above was observed with this glycal. Ferrier⁹¹ suggested that the reaction of D-glucal triacetate with phenyl mercuriacetate in methanol involved an initial transvinylation equilibrium (XVII→XIX), which may be regarded as proceeding through the intermediate adduct (XVIII). The double bond in the open chain triacetate (XIX) would then migrate to the 2,3-position with the simultaneous displacement of the 3-acetate group as acetic acid to give the cis 2,3-unsaturated dimethyl-acetal product (XX). This latter step could occur either

directly or through the intermediate adduct (XXI). The direct migration of the double bond (XIX→XX) might be expected to occur readily because Ness and Fletcher⁹² have reported that a similar migration of a double bond in an unsaturated furanose derivative was complete within 24 hours at room temperature.



The trans 2,3-unsaturated dimethylacetal (XXII) might also be expected to be formed in the reaction by a similar mechanism.



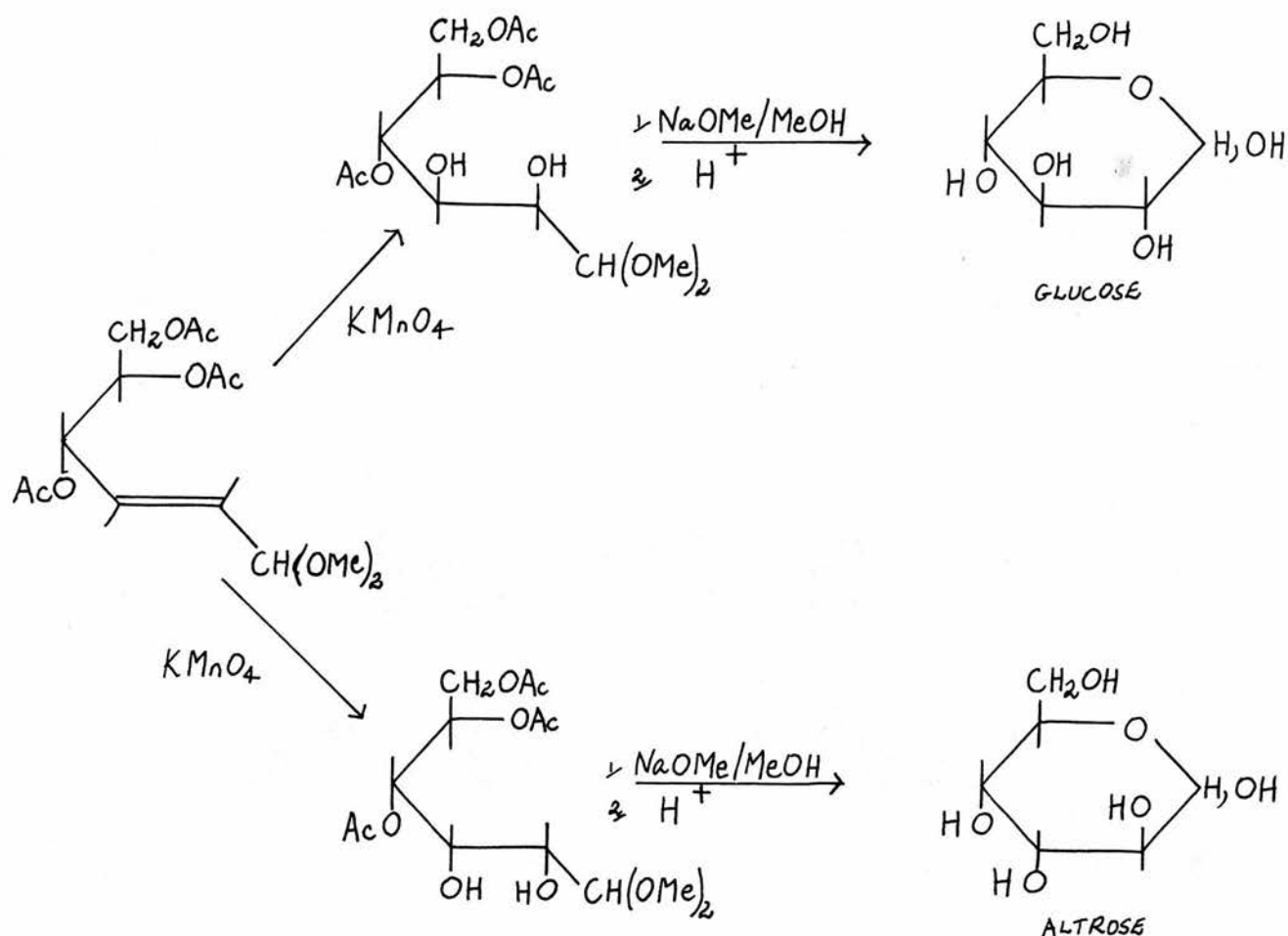
As mentioned earlier, this modification of the glycal has also been observed with the β -D-gluc_o-mercurial (II; $\text{R} = \text{Ac}$, $\text{X} = \text{OAc}$) in place of phenyl mercuriacetate. In the former case,

the reaction would proceed via an intermediate similar to (XVIII) in which the phenyl on the mercury was replaced by a glucose residue. It is interesting to note that this intermediate is of an identical type to the his mercurial already postulated as the intermediate in the transmercuration reaction.

The experimental data for the reaction of D-glucal triacetate with phenyl mercuriacetate in methanol will now be reconsidered in the light of Ferrier's proposals. One mole of acetic acid would be formed by his mechanism which is in accordance with the experimental observations. Furthermore, partially acetylated sugar derivatives would be produced which agrees with the difference in the chromatographic properties observed between the product (A) and the acetylated product (C). The formation of the trans 2,3-unsaturated aldehyde and the monosubstituted furan by the addition of acid to the acetylated and deacetylated products respectively, would suggest the presence of trans and cis 2,3-unsaturated acetals in the products. (A weakness in this latter argument will be discussed later.)

The appearance of glucose and altrose in the acid hydrolysed oxidation product was disturbing on our earlier hypothesis because these sugars have a trans diol arrangement on C₍₂₎ and C₍₃₎. This result can now be accounted for if the presence of the trans unsaturated acetal (XXII) is assumed in the reaction product since cis addition to this compound can give products having either the glucose or altrose configuration,

as shown below:

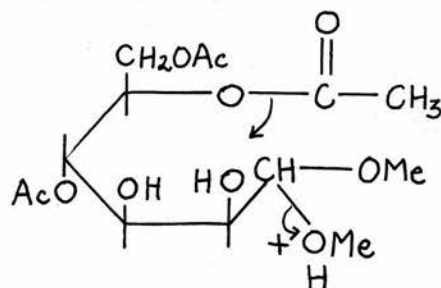


Since the dimethylacetal grouping is known to be very acid sensitive, it would be expected that the removal of the acetal group and subsequent ring closure to give glucose and altrose would occur readily under the conditions of acid hydrolysis. This scheme would account for the fact that methyl glucoside or altroside did not appear to be present in the oxidation product prior to acid hydrolysis.

The appearance of mannose in the acid hydrolysed oxidation product cannot be explained by a similar cyclisation of the oxidised cis acetal (XX) during acid hydrolysis, because methyl

α -D-mannopyranoside has been isolated from the deacetylated oxidation product prior to acid treatment. Furthermore, paper chromatography on the oxidation product after acetylation suggested the presence of the glycoside tetraacetate. Several mechanisms have been considered for the formation of this glycoside and these will now be discussed.

Examination of the working up procedure of the oxidised product reveals that the product was treated with Amberlite IRC-50 (H^+) ion-exchange resin in an attempt to remove inorganic cations. Ferrier⁹¹ has suggested that the cyclisation of the oxidised cis acetal might have occurred during this acid treatment, as shown below:



Although this mechanism would conveniently explain the presence of the glycoside and its tetraacetate in the oxidation product, there appears to be no precedent for such a mechanism in the literature.

A more likely stage for the cyclisation to occur would be on deionisation with Amberlite IRC-50 (H^+) resin of the methanolic solution after Zemplan deacetylation. Although this explanation would account for the isolation of methyl α -D-mannopyranoside in the deacetylated oxidation product, it

does not explain the appearance of the tetraacetate in the acetylated product. Since, however, the presence of the latter was based on a chromatographic assignment in only one solvent system, this might be a case of mistaken identity.

Another possible explanation may be that acetyl migration of the C₍₅₎ acetyl group might have occurred under the oxidation conditions. Thus, since the oxidation solution became distinctly alkaline (i.e. pH ca. 10 to Universal Indicator paper) due to the formation of potassium bicarbonate, the occurrence of acetyl migration would not be surprising under these conditions. The cyclisation of the oxidised dimethyl-acetal on treatment of the oxidation solution with acid ion-exchange resin prior to acetylation would be extremely attractive if a free hydroxide group on C₍₅₎ was postulated.

The above discussion indicates that the cis and trans unsaturated acetals (XX) and (XXII), proposed as the products of the reaction of D-glucal triacetate with phenyl mercuri-acetate, appear to explain a great deal of the experimental results. However, there are certain other aspects of the results which cannot be satisfactorily explained and these will now be considered.

If the product (C) consisted of a mixture of the cis and trans unsaturated acetals, then a methoxide content of 19.5% would be expected; the observed value was found to be only 14.3%. This low methoxide content was also indicated by examination of the ratios of methoxide protons to other protons

in the N.M.R. spectrum. Thus, if the acetylated product (C) consisted of only the cis and trans acetals, then ratios of 6 : 7 and 6 : 9 would be expected for methoxide protons : ring protons and methoxide protons : acetate protons; the observed ratios were found to be about 6 : 12 and 6 : 14 respectively.

Although the formation of the trans 2,3-unsaturated aldehyde and the monosubstituted furan have been conveniently explained earlier as arising from the acid decomposition of the unsaturated trans and cis acetals respectively, there is an inherent weakness in this argument. Thus, it might have been expected that the cis unsaturated aldehyde should also have been observed on the addition of acid to the acetylated product, since ring closure is no longer possible. Furthermore, it is strange that the trans unsaturated aldehyde could not be detected in the acid treated product (B) since ring closure of this aldehyde does not appear likely.

The above discussion has shown that although the postulate, that the cis and trans unsaturated acetals (XX and XXII resp.) are the products of the reaction of D-glucal triacetate with phenyl mercuriacetate in methanol, goes a good way to explaining the experimental results, this does not appear to be the complete answer. It is unfortunate that time did not permit us to proceed further with this work in order that the exact nature of this interesting reaction could be understood. In particular, it is clearly very desirable that the unsaturated products should be isolated individually from the mixture, so that their reactions can be studied unambiguously.

B. Studies on the Deacetylation of Sugar-O-Acetates with Sodium Acetate in Methanol.

It was noted in Part III, A of this thesis that methyl 2-acetoxymercuri-2-deoxy- β -D-glucopyranoside triacetate (II; R = Ac, X = OAc) underwent a slow reaction in methanol as was shown by the fall in the optical rotation. This reaction was examined further and it was found that deacetylation of the mercurial had occurred under these conditions because methyl 2-chloromercuri-2-deoxy- β -D-glucopyranoside triacetate (II; R = Ac, X = Cl) was isolated on acetylation of the reaction product after conversion to the mercurichloride.

A similar deacetylation to the above was also observed on passage of the product from the reaction of phenyl mercuri-acetate on D-glucal triacetate through a column of Amberlite IRC-50 (Na^+) ion-exchange resin (Part III, A). Since sodium acetate was produced on the column, it was suggested that this salt was the cause of the deacetylation; the removal of the acetate groups was thought to involve a transesterification reaction, catalysed by methoxide ion which was produced by the interaction of the acetate ion from sodium acetate with the solvent, as shown below:



In confirmation of this, methanolic sodium acetate has been shown to be an efficient deacetylating agent because methyl

α -D-glucopyranoside was obtained in almost quantitative yield on treatment of the tetraacetate with this reagent. The kinetics of this deacetylation reaction have been studied to ascertain its mechanism, and this work will now be considered.

The rates of deacetylation were determined by observing the change in the optical rotation on treatment of methyl α -D-glucopyranoside tetraacetate with various concentrations of sodium acetate in methanol. This glycoside was suitable for rate studies by this means because a large change in the optical rotation occurred on deacetylation. Since deacetylation of the tetraacetate was also observed with methanolic sodium acetate in the presence of acetic acid, this eliminates the possibility that the deacetylation was caused by traces of alkali in the sodium salt. Determinations of the rates of deacetylation of the glycoside by methoxide ion from sodium methoxide have also been performed for comparison with the sodium acetate results.

An interesting feature of the kinetic determinations was that the rotation of the solution remained steady for a period after mixing of the reagents. This "induction period", I , is clearly shown in Graph B at the end of this section. Although the subsequent reaction is undoubtedly complex, the change in rotation occurring gives a linear first-order plot and it seems not unreasonable to assume that the rate constant thus obtained gives an approximate measure of the "deacetylating power" of the solution (however, the possibility that an acetyl

migration, rather than a deacetylation, controls the rotation change cannot be excluded). Two typical runs (one fast and one slow), which serve to illustrate the linear plots obtained by this method are shown at the end of this section (Graphs A and B).

First-order rate constants were derived from the rate data by the usual method of plotting $\log_{10} (a_t - a_\infty)$ vs. t , the slope of the straight line obtained being equal to $-k/2.303$. The rate constants for the various determinations are shown in Table I along with the methoxide ion concentration of each solution which was calculated from the autoprotolysis constant of methanol ($k_{\text{MeOH}} = 2.1 \times 10^{-17}$)⁹³ and the ionisation constant of acetic acid in methanol ($k_{\text{AcOH}} = 2.4 \times 10^{-10}$),⁹⁴ as shown below:

$$\begin{aligned} \frac{[\text{MeO}^-][\text{HOAc}]}{[\text{OAc}^-]} &= [\text{MeO}^-][\text{H}^+] \times \frac{[\text{HOAc}]}{[\text{H}^+][\text{OAc}^-]} \\ &= \frac{k_{\text{MeOH}}}{k_{\text{AcOH}}} = \text{ca. } 9 \times 10^{-8} \\ [\text{MeO}^-] &= \frac{9 \times 10^{-8} [\text{OAc}^-]}{[\text{HOAc}]} \end{aligned}$$

It was found that the induction period I was proportional to the half-life time of the reaction, i.e., $t_{1/2}/I = \text{ca. } 5$, for deacetylations with sodium acetate and sodium methoxide. Thin-layer chromatography on the reaction solution during the induction period showed the presence of small amounts of deacetylated materials and this result indicates that no change in the optical rotation accompanies the initial deacetylation of

Table I

The Rates of Deacetylation of Methyl α -D-glucopyranoside
Tetraacetate (0.1M) in Methanol.

Deacetylating Agent	$[OMe^-]$ M	Rate Constant k sec. ⁻¹	$[OMe^-]/k$ = k'
1. 1M-NaOAc	3.0×10^{-4}	8.1×10^{-5}	3.7
2. 1M-NaOAc in CO ₂ free-MeOH	3.0×10^{-4}	1.0×10^{-4}	3.0
3. 1M-NaOAc in MeOH ($\frac{1}{2}$ satd. with CO ₂)		1.1×10^{-6}	
4. 1M-NaOAc + methyl α -D-glucopyranoside (0.1M)	3.0×10^{-4}	4.0×10^{-5}	7.5
5. 1M-NaOAc in MeOH containing 0.5% H ₂ O	3.0×10^{-4}	8.1×10^{-5}	3.7
6. 1M-NaOAc + 0.1M-HOAc	9.0×10^{-7}	3.2×10^{-7}	2.8
7. 1M-NaOAc + 0.01M-HOAc	9.0×10^{-6}	2.8×10^{-6}	3.2
8. 1M-NaOAc + 0.001M-HOAc	8.5×10^{-5}	2.4×10^{-5}	3.5
9. 0.1M-NaOAc	9.5×10^{-5}	6.9×10^{-6}	13.8
10. 0.01M-NaOAc	3.0×10^{-5}	1.0×10^{-6}	30.0
11. 0.01M-NaOAc in CO ₂ free-MeOH	3.0×10^{-5}	0.9×10^{-6}	33.2
12. 0.01M-NaOAc + 1M-NaI	3.0×10^{-5}	0.5×10^{-6}	60.0
13. 1×10^{-3} M-NaOMe	1.0×10^{-3}	3.8×10^{-4}	2.6
14. 1×10^{-3} M-NaOMe + 1M-NaOAc	1.1×10^{-3}	9.5×10^{-4}	1.2
15. 1×10^{-3} M-NaOMe + 1M-NaI	1.0×10^{-3}	4.0×10^{-4}	2.5
16. 3×10^{-4} M-NaOMe	3.0×10^{-4}	4.4×10^{-5}	6.8
17. 1×10^{-4} M-NaOMe	1.0×10^{-4}	4.0×10^{-7}	250
18. 0.1M-PhHgOAc		1.1×10^{-6}	

the glycoside tetraacetate.

The possibility that the accumulation of deacetylated products in the induction period autocatalyses the subsequent reaction is excluded by the fact that the kinetics were essentially unchanged when fresh methyl α -D-glucopyranoside tetraacetate was added to a solution in which the deacetylation had been completed (cf. expts. 1 and 4, Table I).

Discussion of the Kinetic Results.

A first-order dependence of the rate of deacetylation on the methoxide ion concentration has been observed in $1M$ -sodium acetate solutions, with or without acetic acid being present (expts. 1, 6, 7 and 8). The ratio of the calculated methoxide ion concentration to the first-order rate constant ($[OMe^-]/k = k'$) was approximately constant for these solutions, even though the former ranged from 3.0×10^{-4} to $9.0 \times 10^{-7}M$. This is in good agreement with the view that the methoxide ion is responsible for the deacetylation.

Examination of the runs 1, 9 and 10 in Table I, however, indicates that the value of k' is dependent upon the concentration of sodium acetate in the solution. Thus, it has been found that k' has a value of ca. 4 in $1M$ -sodium acetate solutions, ca. 14 in a $0.1M$ -solution and ca. 30 in a $0.01M$ -solution. This dependence of k' on the concentration has also been observed in deacetylations catalysed by methoxide ion from sodium methoxide (expts. 13, 16 and 17). An attempt has been made to establish the cause of this variation with concentration, and the following possibilities were examined:

- (a) an ionic strength effect (b) catalysis by acetate ion
 (c) retardation by an impurity in the methanol.

(a) An ionic strength effect. The variation of k' with the sodium acetate concentration was taken initially to suggest the dependence of the rate of deacetylation upon the ionic strength of the solution. This possibility can be eliminated, however, because it was found that the rate constants for deacetylations with $0.01M$ -sodium acetate solution and $1 \times 10^{-3}M$ -sodium methoxide solution were not appreciably increased by altering the ionic strength of the solutions by the addition of sodium iodide (cf. expts. 10 and 12, and expts. 13 and 15). This indicates the independence of k' on the ionic strength of the solution.

(b) Catalysis by acetate ion. If acetate catalysis occurred in deacetylations with sodium acetate, it would have a greater effect in strong solutions ($1M$) than in the more dilute solutions ($0.1M$ and $0.01M$) and thus might explain the variation of k' with concentration.

The rate of deacetylation with a mixture of sodium methoxide ($1 \times 10^{-3}M$) and sodium acetate ($1M$) was determined to ascertain whether acetate catalysis was significant. Since the methoxide ion contribution derived from the sodium acetate in this solution would be negligible, then the rate constant for this solution should be similar to that found for $1 \times 10^{-3}M$ -sodium methoxide. It was found, however, that the rate constant for the mixture was ca. 2 times faster than for sodium methoxide alone (cf. expts. 14 and 13) and this suggests that acetate ion

catalysed deacetylation may occur in the former reaction. However, the magnitude of this acetate catalysis would appear to be too small to account for the large change observed in k' with concentration.

(c) Retardation by an impurity in the methanol. The possibility that the variation of k' with concentration was caused by the presence of a constituent in the methanol was examined.

Kinetic experiments were performed initially in methanol which had been dried by distillation over magnesium methoxide.⁵⁵ These results were rejected, however, when it was later found that methyl α -D-glucopyranoside tetraacetate underwent a slow deacetylation in this solvent which was attributed to the presence of traces of magnesium methoxide. Whitaker, Tate and Bishop⁹⁵ have already observed this deacetylating action of magnesium methoxide-dried methanol. Since precautions were taken to prevent any of the solvent being distilled from splashing over into the distillate, this indicates that magnesium methoxide must be slightly volatile, or else is carried over as a fine spray with the methanol.

In an attempt to remove the basic salts from the dried methanol above, the latter was distilled in the presence of 2,4,6-trinitrobenzoic acid.⁹⁶ It was found, however, that the distillate contained some of this acid which could be detected by the yellow colour which it gave with sodium. Although the acid appeared to be removed by a further distillation, the rates of deacetylation with sodium acetate, and with sodium

methoxide, in this solvent were found to be appreciably slower than those observed for similar deacetylations in either magnesium methoxide-dried methanol or redistilled magnesium methoxide-dried methanol (e.g. the rate constant observed for deacetylation with 1M -sodium acetate in this solvent was 4.0×10^{-5} ; cf. expt. 1). This result suggests the persistence of traces of the acid in the methanol which are not removed by redistillation.

The methanol used for the kinetic experiments described in Table I was dried by distillation from magnesium methoxide and redistilled. It was found that methyl α -D-glucopyranoside tetraacetate, dissolved in this methanol, gave no signs of deacetylation after 4 months.

The rate of deacetylation with sodium acetate in methanol was found to be unaffected by the presence of small amounts of water in the solvent (cf. expts. 1 and 5).

Since acid is produced along with methoxide ion in the equilibrium between acetate ion and methanol mentioned earlier, then it would be expected that the presence of acid in the methanol would shift the position of the equilibrium to the left and thus decrease the methoxide ion concentration. To establish whether traces of acid in the methanol might be the cause of the variation of k' with concentration of sodium acetate, the effect of acetic acid on the equilibrium between acetate ion and methanol was calculated. It was found that an acid concentration as low as ca. $4 \times 10^{-4}\text{M}$ in the methanol

was sufficient to account for the variation observed for k' . Thus, if this acid concentration was assumed in the methanol, then k' appeared to be almost independent of the sodium acetate concentration. Although acetic acid was assumed to be the acid present in the methanol in these calculations, formic acid would be more likely. However, the effect of formic acid on the equilibrium cannot be calculated because the ionisation constant of formic acid in methanol does not appear in the literature.

Although the above results suggest that the presence of a trace of acid in the methanol might be the cause of the variation of k' with sodium acetate concentration, this does not appear to be the complete answer because a similar variation of k' has been observed in methanol which is basic due to traces of magnesium methoxide.

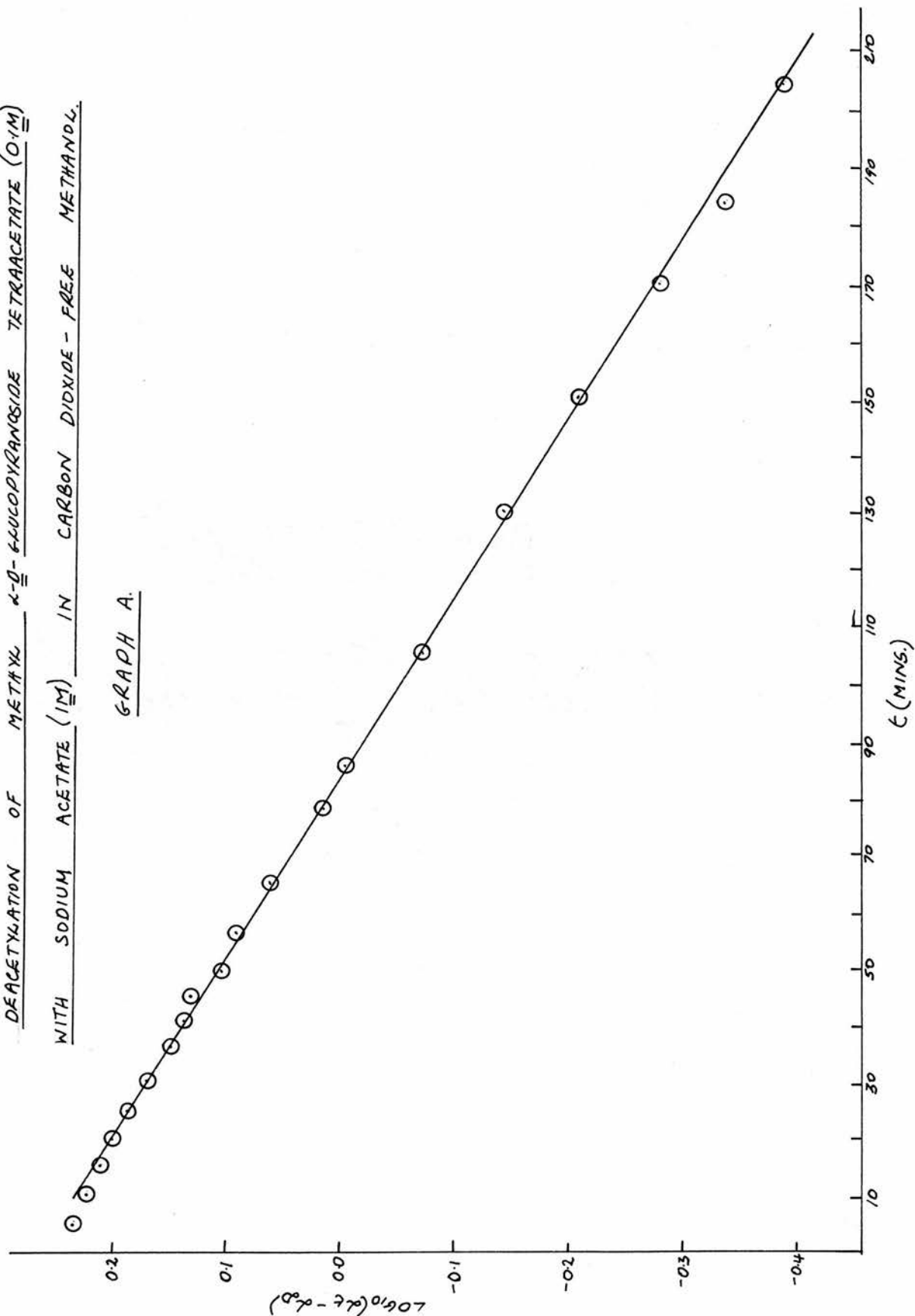
To ascertain whether the presence of carbon dioxide in the methanol would have an effect on the rate constants, the reaction of methyl α -D-glucopyranoside tetraacetate in methanol which was half-saturated with carbon dioxide was studied. It was found that the rate constant for this reaction was reduced to about one hundredth of the rate constant in carbon dioxide-free methanol (cf. expts. 3 and 2; the carbon dioxide-free methanol was prepared by passage of dry nitrogen into the methanol for several hours). It was found, however, that the rate constants for deacetylation with 1M and 0.01M -sodium acetate were essentially unchanged on performing the reactions

in this carbon dioxide-free methanol (cf. expts. 1 and 2, and expts. 10 and 11).

Although the above results have shown that the value of k' can be greatly affected by mere traces of constituents in the methanol, the variation found for sodium acetate solutions of different concentrations remains in doubt.

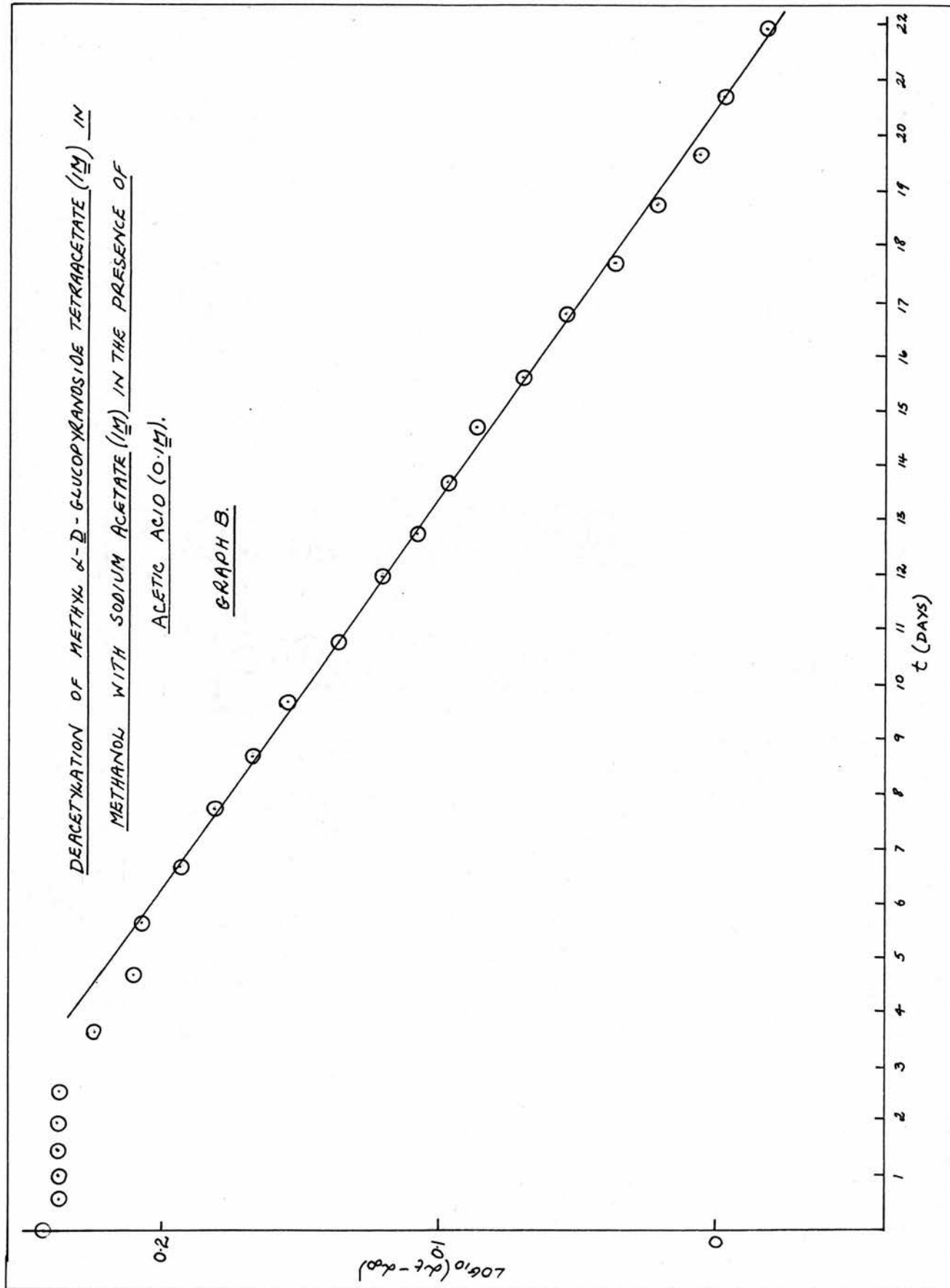
DEACETYLATION OF METHYL α -D-GLUCOPYRANOSIDE TETRAACETATE (0.1M)
WITH SODIUM ACETATE (1M) IN CARBON DIOXIDE - FREE METHANOL.

GRAPH A.



DEACETYLATION OF METHYL α -D-GLUCOPYRANOSIDE TETRAACETATE (1M) IN
METHANOL WITH SODIUM ACETATE (1M) IN THE PRESENCE OF
ACETIC ACID (0.1M).

GRAPH B.



EXPERIMENTAL(1) Optical and Chromatographic Data for the Experiments involving the Reaction of a Glycal with a Glycal Mercuration Product.

Numerous preliminary experiments were performed in an attempt to understand the nature of the reaction occurring on the addition of a glycal to a glycal mercuration solution. Since later work showed that there were several reactions taking place under these conditions, only the observed rotation changes and the chromatographic results for these reactions will be given here.

In each experiment, a glycal triacetate (0.300 g., 1.10 mmoles) in methanol (2 ml.) was treated with mercuric acetate (0.352 g., 1.10 mmoles) in methanol (8 ml.). After a steady rotation was attained, excess of this or another glycal triacetate (0.300 g.) in methanol (5 ml.) was added and the rotation of this solution recorded at intervals in a 2 dm. tube. When the reaction was complete, sodium chloride (0.07 g., 1.20 mmoles) in water was added to convert the mercurials to the mercuri-chloride. After removal of solvents by evaporation, the carbohydrate material was obtained by extraction into chloroform and evaporation of the dried organic layer. Paper chromatography on the syrupy mixture thus obtained was performed in solvent (vii), spray (c).

The following experiments were performed:

(i) D-glucal triacetate mercuration solution + D-galactal triacetate; $\alpha +0.12 \rightarrow +3.30^\circ$ (3-4 weeks); paper chromatography showed the α -D-talo-mercurial (IX; R = Ac, X = Cl) (R_F ca. 0.50) to be the chief product together with the α -D-manno-mercurial (I; R = Ac, X = Cl) (R_F ca. 0.44), and a trace of the β -D-gluco-mercurial (II; R = Ac, X = Cl) (R_F ca. 0.38).

(ii) D-galactal triacetate mercuration solution + D-glucal triacetate; $\alpha +2.10 \rightarrow +1.70^\circ$ (3 weeks); paper chromatography gave identical results to those observed in (i) above.

(iii) D-glucal triacetate mercuration solution + D-glucal triacetate; $\alpha -0.75 \rightarrow 2.40^\circ$ (3-4 weeks); paper chromatography indicated that the α -D-manno-mercurial was the chief product, together with a trace of the β -D-gluco-isomer.

(iv) D-galactal triacetate mercuration solution + D-galactal triacetate; $\alpha +3.04 \rightarrow +3.40^\circ$ (3-4 weeks); paper chromatography indicated that the α -D-talo-isomer was the only mercurial present.

In another experiment, D-glucal triacetate (0.272 g., 1.00 mmoles) was added to methyl 2-acetoxymercuri-2-deoxy- β -D-glucopyranoside triacetate¹⁰ (0.563 g., 1.00 mmoles) in methanol (11 ml.). The optical rotation of this solution in a 1 dm. tube rose from a value of $+0.40^\circ$ to a steady value of $+1.50^\circ$ in 4 weeks, one mole of acetic acid being produced. Paper chromatography in solvent (vii), sprays (a) and (c), on the product (A'), after conversion to the mercurichloride, indicated the presence of the α -D-manno-mercurial (R_F ca. 0.44), a trace of the β -D-gluco-isomer (R_F ca. 0.38), together with mercury-free

constituents at R_F ca. 0.51 and ca. 0.55. In addition, there were traces of several slower moving mercury products (R_F ca. 0.10, 0.16 and 0.25) which probably correspond to partially acetylated products. It is of interest to note that the chromatographic properties of the mercury-free materials in this product (A'), in the deacetylated product (B'), and also in the product (C') obtained on acetylation of (A') and (B'), are identical to those in the corresponding products (A), (B) and (C) obtained from the reaction of phenyl mercuriacetate with this glycal.

(2) The Reaction of Methyl 2-acetoxymercuri-2-deoxy- β -D-glucopyranoside Triacetate¹⁰ with Methanol.

The mercurial (0.083 g., 0.15 mmoles) underwent a slow reaction in methanol (1.5 ml., the methanol used was magnesium methoxide-dried and redistilled) as was shown by the fall in the optical rotation of the solution (α in 1 dm. tube $+0.49 \rightarrow -0.16^\circ$ in 2 weeks). Silica Gel thin-layer chromatography, in ethanol-benzene (1 : 3), spray (d), on the completed reaction solution after conversion to the mercurichloride indicated that the acetylated mercurial had completely reacted to give a product with a mobility corresponding to methyl 2-chloromercuri-2-deoxy- β -D-glucopyranoside¹⁰ (R_F 0.24), together with small amounts of faster moving partially acetylated products. The chromatographic assignment to the reaction product was confirmed by the isolation of its triacetate (0.03 g., 37%), m.p. and mixed m.p. 172° , on acetylation. Paper chromatography, in solvent (vii), sprays (a) and (c), on the mother liquor showed the

presence of this mercurial and a little D-glucal triacetate.

(3) The Reaction of Cyclohexene with Methyl 2-acetoxymercuri-2-deoxy- α -D-mannopyranoside¹¹ in Methanol.

The mercurial (0.654 g., 1.50 mmoles) in methanol (6 ml.) was treated with an excess of cyclohexene (0.50 g., 6.10 mmoles) in the same solvent (2 ml.). The slow reaction which occurred under these conditions was followed by carrying out thin-layer chromatography at intervals on small amounts of the reaction solution to which had been added aqueous sodium chloride to convert the mercurials to the mercurichloride. The reaction was found to be complete within 3 weeks and Silica Gel thin-layer chromatography in ethanol-benzene (1 : 3), spray (d), indicated that three mercurials were present with mobilities in this system corresponding to the α -D-manno-mercurial (I; R = H, X = Cl) (R_F 0.35), the β -D-gluco-isomer (II; R = H, X = Cl)¹⁰ (R_F 0.24) and cyclohexyl α -methoxymercurichloride¹² (R_F 0.80). These assignments were confirmed by paper chromatography in solvent (i), spray (c), the three mercurials present corresponding to the α -D-manno-mercurial (R_F 0.51), the β -D-gluco-mercurial (R_F 0.45) and the cyclohexyl mercurial (R_F 0.85).

The mercurials in the reaction solution were converted to the mercurichlorides by treatment with IRA-400 (Cl⁻) ion-exchange resin, the conversion confirmed by the lanthanum nitrate spot test for acetate⁶⁷ (Experimental, Part I). After removal of methanol by evaporation, the mercurials were taken up in

water (4 ml.) and the cyclohexyl mercurial separated from the sugar mercurials by extraction into benzene (2 x 4 ml.). Evaporation of the organic layer gave cyclohexyl α -methoxymercurichloride (0.06 g.), m.p. and mixed m.p. 114° .¹²

Although a small amount of methyl 2-chloromercuri-2-deoxy- β -D-glucopyranoside¹⁰ could be isolated in the crystalline form, m.p. 167° , by evaporation of the aqueous layer and crystallisation from methanol, it was found more convenient to isolate this mercurial as the less soluble triacetate. Thus, evaporation of the aqueous layer and treatment with acetic anhydride in pyridine gave a syrupy mixture from which methyl 2-chloromercuri-2-deoxy- β -D-glucopyranoside triacetate (0.16 g.), m.p. and mixed m.p. 172° , was obtained on crystallisation from ethanol-acetone. The mother liquor was shown by paper chromatography in solvent (vii), sprays (a) and (c), to consist of this β -D-gluco-mercurial, together with the α -D-manno-isomer and a little D-glucal triacetate.

(4) The Reaction of D-Glucal Triacetate with Phenyl Mercuriacetate in Methanol.

The reaction of D-glucal triacetate (2.00 g., 7.35 mmoles) with phenyl mercuriacetate (2.48 g., 7.38 mmoles) in methanol (30 ml.) was accompanied by a slow rise in the optical rotation (α in 1 dm. tube $-0.75 \rightarrow +3.50^{\circ}$, steady value, in 4 weeks). The N.M.R. spectrum of this solution, which was recorded at intervals in the reaction, showed the gradual disappearance of the characteristic low field $H_{(1)}$ doublet of D-glucal

triacetate.⁹⁷ Titration of the final solution with 0.01N-sodium hydroxide solution indicated that 1 mole of acid had been produced in the reaction (i.e. two equivalents of alkali were consumed, one of which is attributable to the mercuriacetate group of the mercurial). Paper chromatography, in solvent (vii), sprays (a) and (c), on the crude reaction product (A) showed the presence of two mercury-free products at R_F ca. 0.51 and ca. 0.56, together with a little unchanged glycal, R_F ca. 0.70. The N.M.R. spectrum of this product in deuterochloroform showed the presence of two signals in ratio ca. 1 : 2 at τ 6.52 and 6.69 respectively.

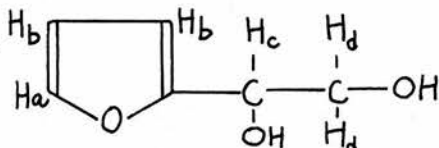
Ion-exchange paper chromatography was performed on product (A) on Amberlite ion-exchange papers with a variety of solvents to discover the optimum conditions for stripping off the mercury salt from the carbohydrate product. It was found that this separation could be easily effected by chromatography on Amberlite WA-2 paper (Na^+ form) with methanol as eluant; the carbohydrate product travelled at the solvent front while the mercurial remained on the starting line. Column chromatography on Amberlite IRC-50 (Na^+) resin was equally effective, a mercury-free product (B), contaminated with sodium acetate, being obtained on evaporation of the eluate. Deacetylation was shown to have occurred on the column because product (B) remained on the starting line on paper chromatography in solvent (vi). Paper chromatography in solvent (i), sprays (b) and (f), showed the presence of three unsaturated constituents at

R_F 0.52, 0.61 and 0.70, the slowest moving of these corresponding to D-glucal. The ultraviolet spectrum of product (B) in water showed a peak at $<190\text{ m}\mu$ (maximum not reached). The N.M.R. spectrum of this material in deuterium oxide showed the presence of two sharp peaks in ratio 1 : 2 at τ 6.57 and 6.67.

Treatment of product (B) with acetic anhydride in pyridine gave a syrupy acetylated product (C) with a methoxide content of 14.3%. The N.M.R. spectrum of product (C) in deuterochloroform showed the presence of two signals at τ 6.56 and 6.74 in a ratio of about 1 : 2. Paper chromatography on this syrup in solvent (vii), spray (a), showed the presence of two constituents at R_F ca. 0.75 and ca. 0.79, together with a little D-glucal triacetate. Paper chromatography in the same solvent system on an authentic α -/ β -glycoside mixture of methyl 4,6-di-O-acetyl-2,3-didehydro-2,3-dideoxy-D-erythro-hexoside alongside product (C) showed the presence in the former of a constituent at R_F ca. 0.40, together with smaller amounts of several slower moving materials; there was no suggestion of any faster moving constituent at R_F ca. 0.75-0.79 corresponding to product (C) in the authentic α -/ β -glycoside mixture.

Acid Decomposition of the Deacetylated Product (B). The deacetylated product (B) was decomposed within 5 minutes in aqueous 0.01N-sulphuric acid, as was shown by the fall in optical rotation and the replacement of the maximum at lower wavelength in the ultraviolet by a peak, $\lambda_{\text{max.}}$ $220\text{ m}\mu$, $\epsilon_{\text{max.}}$ ca. 5000 (furfuryl alcohol in H_2O , $\lambda_{\text{max.}}$ $217\text{ m}\mu$, $\epsilon_{\text{max.}}$ 8000). The

value ϵ_{\max} . for the decomposition solution was calculated assuming that all the product (B) consisted of the furan. The N.M.R. spectrum of this decomposition solution, after deuteration to remove water, showed the following peaks and relative intensities: singlet τ 2.50, taken as one proton, $H_{(a)}$; singlet τ 3.60, two protons, $H_{(b)}$; triplet τ 5.23, spacing = 6 c.p.s., three protons, $H_{(c)}$; doublet τ 6.10, spacing = 6 c.p.s., three to four protons, $H_{(d)}$. The triplet at τ 5.23 could only be detected in deuterium oxide which was saturated with sodium chloride to shift the position of the water peak. The chemical shifts and multiplicities of these signals suggest the presence of the monosubstituted furan



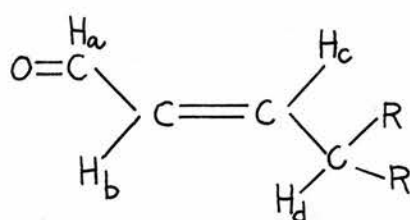
decomposition solution. The chemical shifts assigned to $H_{(a)}$, $H_{(b)}$ and $H_{(c)}$ are almost identical to those of the corresponding protons in furfuryl alcohol,⁵⁴ and the chemical shift for the $H_{(d)}$ doublet is similar to the terminal protons of D-glycerol.⁵⁴

Periodate oxidation was performed on the above acid decomposed solution and the oxidised solution was distilled; furfuraldehyde was detected in the distillate by its characteristic ultraviolet spectrum, λ_{\max} . 230 and 277 $m\mu$, $\epsilon_{277}/\epsilon_{230} = 3.6$ (furfuraldehyde λ_{\max} . 230 and 278 $m\mu$, $\epsilon_{278}/\epsilon_{230} = 3.8$).

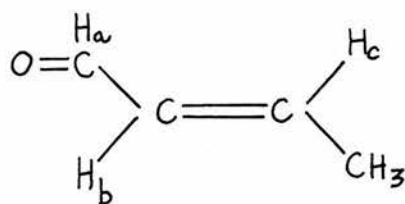
Examination of the N.M.R. intensities of the spectrum suggested the presence of another constituent in a similar amount to the furan. Since the signals of this material appeared

in the region τ 4.0-6.5, they were partially masked by the more pronounced peaks of the furan and thus no analysis could be made. It is the presence of this unidentified constituent in the decomposition solution which accounts for the intensity discrepancy observed above for the signals of the furan protons.

Acid Decomposition of the Acetylated Product (C). Decomposition of the acetylated product (C) in 0.01N-sulphuric acid in aqueous ethanol (1 : 1) resulted in the immediate appearance of a peak, $\lambda_{\text{max.}}$ 210 $m\mu$ in the ultraviolet. The N.M.R. spectrum of the decomposition product after extraction into deuteriochloroform was complex but analysis of the pattern of peaks at low field, remote from the remainder of the spectrum, suggested that a trans 2,3-unsaturated aldehyde was present because of the close similarity with the spectrum of trans crotonaldehyde.⁵⁴



Decomposition
product.



trans
crotonaldehyde.

γ Values
and Coupling
Constants.

$H_{(a)}$	0.38 (doublet)	0.52 (doublet)
$H_{(b)}$	3.72 (quartet)	3.87 (quartet)
$H_{(c)}$	3.16 (quartet)	3.13 (two quartets)
J_{ab}	7 c.p.s.	7 c.p.s.
J_{bc}	16 c.p.s.	16 c.p.s.
J_{cd}	5 c.p.s.	6 c.p.s.

The observation that $H_{(c)}$ appears as a quartet in the decomposition solution indicates the presence of one proton, $H_{(d)}$, on the 4-carbon atom in the unsaturated aldehyde. Furthermore, the broadening which was observed for the $H_{(b)}$ quartet may be caused by allylic coupling with $H_{(d)}$, but this cannot be stated with certainty because of the high "noise" level of the spectrum.

Calculation of the N.M.R. intensities of the spectrum of the acid decomposed product (C) suggested that the aldehyde constituted about one third of the product.

Permanganate Oxidation of Product (C). Product (C) was oxidised under neutral conditions with aqueous potassium permanganate according to the procedure of Ferrier, Overend and Ryan.⁹⁰ After destroying the slight excess of permanganate by addition of ethanol, the solution was treated with Amberlite IRC-50 (H^+) ion-exchange resin. This resin treatment did not completely remove the inorganic cations from the solution and it was necessary to acetylate this oxidised product by treatment with acetic anhydride in pyridine. Paper chromatography in solvent (vi), spray (a), on the acetylated product thus obtained showed the presence of a constituent with a mobility identical to that of methyl α -D-mannopyranoside tetraacetate (R_F ca. 0.60), together with several other constituents (R_F 0.67, 0.54 and 0.40). Deacetylation of this oxidised material gave a syrupy mixture which was shown by paper chromatography in solvent (i), spray (b), to consist of methyl α -D-mannopyranoside (R_F 0.35),

together with several other constituents which were not identified (R_F 0.44 and 0.19). The presence of methyl α -D-mannopyranoside was confirmed by the isolation of a small amount of the glycoside in the crystalline form, m.p. and mixed m.p. 193-195°, by chromatography on a column of IRA-400 (OH^-) ion-exchange resin with water as eluant. No appreciable separation of the other constituents in the deacetylated oxidation product could be effected by this means.

The deacetylated product from a similar oxidation, without isolation of methyl α -D-mannopyranoside, was heated with 1N-hydrochloric acid at 100° for four hours. After neutralisation with silver carbonate, a syrupy mixture was obtained which was shown by paper chromatography in solvents (i), (iii), (iv) and (v), spray (b), to consist of similar amounts of glucose, mannose and altrose.

(5) The Kinetics of the Deacetylation of Methyl α -D-glucopyranoside Tetraacetate.

(i) Reagents. The methanol used for the kinetic experiments was of A.R. quality, which was dried by distillation from magnesium methoxide⁵⁵ and then redistilled.

Sodium acetate used in the deacetylations was of A.R. quality, which was dried at 130° for 12 hours in vacuo over phosphorus pentoxide before use. Titration of this dried reagent to pH 8.8 with 0.01N-sulphuric acid using a pH meter indicated that negligible free acid or alkali were present (i.e. free alkali present consumed not more than 0.1 ml. N-acid per cent).⁹⁸

Sodium methoxide reagent was freshly prepared by dissolving sodium in methanol under nitrogen and estimation of the concentration of the solution by titration against standard acid.

Methyl α -D-glucopyranoside tetraacetate, m.p. 100° , $[\alpha]_D^{+130^{\circ}}$ (CHCl_3) was prepared by treatment of methyl α -D-glucopyranoside with sodium acetate and acetic anhydride at 100° according to the procedure of Konigs and Knorr.⁹⁹

(ii) Measurement of the reaction rates. The reactions were followed by observing the change in the optical rotation in a 1 dm. tube of a solution of methyl α -D-glucopyranoside tetraacetate (0.362 g., 1.00 mmoles) and the deacetylating agent in methanol (10 ml., total volume). Silica Gel thin-layer chromatography in ethanol-benzene (1 : 3), spray (g), could be carried out at intervals in the reaction to give an indication of the extent of deacetylation. Methyl α -D-glucopyranoside travelled at R_F 0.10 in this solvent system and the tetraacetate at R_F 0.75; the partially deacetylated sugars had intermediate R_F values.

Examination of those rate determinations in Table I, which were repeated under essentially similar conditions, indicates that a fair reproducibility of the results is to be expected by this method. It must be emphasised, however, that the rate constants determined by this method were dependent to a large extent on the method of drying the solvent. However, although slightly different values for the rate constants were observed in acidic methanol, and in methanol which was basic due to traces of magnesium methoxide, the same general pattern of the

rate constants to those given in Table I was obtained in each case.

(iii) The separation of methyl α -D-glucopyranoside from sodium acetate. This separation can be easily effected by chromatography on a charcoal/celite column. Sodium acetate was completely removed from the column by elution with water, while 10% aqueous ethanol was necessary to strip off the glycoside. By this means an almost quantitative yield of methyl α -D-glucopyranoside was obtained from the reaction solution in which the deacetylating agent was LM-sodium acetate (expt. 1, Table I).

PART IVStudies on the Optical Rotations of Sugars.

Although the phenomenon of optical activity was discovered by Biot¹⁰⁰ in 1815 and became a powerful tool in the hands of chemists by the end of the century, it remained until the second quarter of this century before a fundamental understanding of the phenomenon was elaborated on the basis of classical and quantum mechanical treatments. The theories of optical rotation thus obtained have been able to predict the magnitude of the optical rotation of certain simple compounds; however, their application to more complicated structures does not appear promising at the present time. Recently, however, Brewster¹ has devised an empirical approach to the relationship between optical rotation and structure, for which he proposes the name: "Conformational Dissymmetry Rule".^{1e} This Rule, which involves a comparatively small number of empirical parameters, allows the prediction of the sign and approximate magnitude of the rotation of many open chain and cyclic compounds, such as carbohydrates^{1b}, steroids^{1b}, alkaloids^{1e}, terpenes^{1b}, endocyclic unsaturated^{1c} and deuterium compounds.^{1d} Before proceeding further, the essential features of this Rule will be discussed briefly.

The Conformational Dissymmetry Rule relates optical rotation to the dissymmetry of polarisability in the molecule and an

important feature of the Rule is the appreciation of the importance of conformational dissymmetry in optical rotation calculations. Brewster^{1a} proposes that the units of conformational dissymmetry, (i) and (ii), Figure I, make a dextrorotatory contribution to the molecular rotation which is $\Delta[M]_D = 160 \sqrt{R_a R_{a'}}$, where R_a and $R_{a'}$ are the atomic refractivities of the attached atoms a and a' (i.e. functions of their polarisabilities). The units (iii) and (iv) in Figure I make corresponding laevorotatory contributions to the rotation.

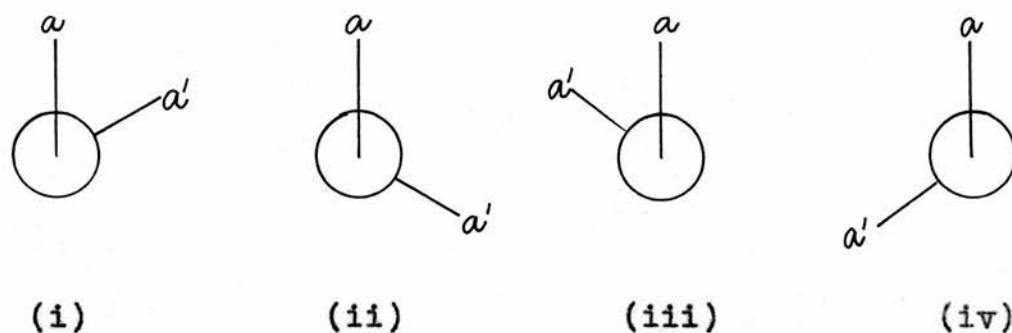
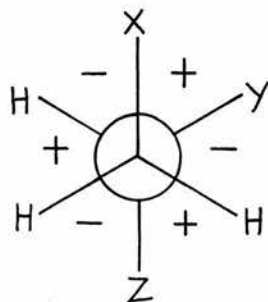


Figure I

Furthermore, the rotatory power of the full conformation (Figure II) is the sum of the rotatory contributions of the six constituent conformational units.



$$\begin{aligned}
 [M]_D &= k(XY - HY + HH - HX) \\
 &= k(X - H)(Y - H)
 \end{aligned}$$

Figure II

Numerical values for the product $k(X - H)(Y - H)$, which were

evaluated empirically from suitable compounds of known rotations, or evaluated from atomic refractivities, are shown in Table I. Brewster¹ employs the empirical values in his calculations on optical rotations.

Table I

Conformational Rotatory Powers.

X	Y	k(X - H) (Y - H)	
		<u>Calculated</u>	<u>Empirical</u>
CH ₃	CH ₃	60°	60°
CH ₃	OH	23°	50°
OH	OH	9°	45°

In addition to the above rules Brewster^{1a} makes certain assumptions relevant to the conformational analysis of open-chain compounds which need not be considered here.

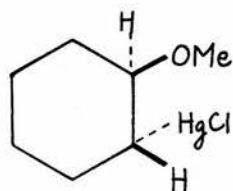
With this brief discussion of the underlying principles of the Conformational Dissymmetry Rule we may now consider the application of this Rule to the rotations of certain sugar derivatives.

The Application of the Conformational Dissymmetry Rule to the Optical Rotations of the Sugar Methoxymercurials.

Sokolov and Reutov¹⁵ applied the Conformational Dissymmetry Rule to the calculation of the rotations of a few optically active compounds containing a mercury atom attached to an asymmetric carbon atom. Thus, using a value of $k(\text{C} - \text{H}) (\text{Hg} - \text{H}) = 246^\circ$, calculated from the atomic refractivities of carbon,

hydrogen and mercury, these workers were able to calculate the rotation of 2-bromomercuributane and thus show that the asymmetric atom had the absolute configuration R.

This successful application of the Rule led these workers to use this method to elucidate the stereochemistry of methoxymercuriation addition to an olefin, cyclohexene, by comparison of the calculated and experimental values for the molecular rotations of the optically active cyclohexyl α - and β -methoxymercurials¹² (Introduction), shown below:

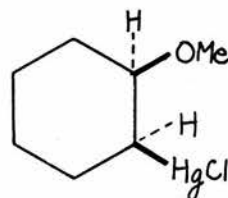
 α -isomer

$$[M]_{\text{expt.}} = -139^{\circ}$$

$$[M]_{\text{calc.}} = -k(\text{Hg} - \text{H})(\text{O} - \text{H})$$

$$= -130^{\circ} \text{ for the diequatorial conformer.}$$

$$[M]_{\text{calc.}} = 0 \text{ for the diaxial conformer.}$$

 β -isomer

$$[M]_{\text{expt.}} = +45^{\circ}$$

$$[M]_{\text{calc.}} = -130^{\circ} \text{ for axial OMe, equat. HgCl conformer.}$$

$$[M]_{\text{calc.}} = +130^{\circ} \text{ for axial HgCl, equat. OMe conformer.}$$

In calculating the value of $k(\text{Hg} - \text{H})(\text{O} - \text{H})$ these workers used a value of $k(\text{C} - \text{H})(\text{O} - \text{H}) = 32^{\circ}$, which they obtained from the refractivities of the individual atoms. It is appropriate to mention here that the value of the latter product is appreciably smaller than the empirical value used by Brewster

in all his calculations (see Table I).

On the basis of the above results, Sokolov and Reutov¹⁵ proposed that the α -mercurial obtained by direct mercuriation had the trans diequatorial structure shown, while the mercury epimerised β -isomer had the cis structure, with the axial HgCl-equatorial OMe conformer predominating.

The optical properties of the methoxymercuration adducts of D-glucal and its triacetate are extremely interesting and warrant further investigation. Thus, the acetylated β -D-gluco-mercurial (II; R = Ac, X = Cl) has a positive rotation ($[\text{M}]_{\text{D}} +59^{\circ}$) while the α -D-manno-isomer (I; R = Ac, X = Cl) is strongly laevorotatory ($[\text{M}]_{\text{D}} -200^{\circ}$). The anomalous rotations are not observed in the deacetylated adducts, the β -D-gluco-mercurial (II; R = H, X = OAc) ($[\text{M}]_{\text{D}} +2^{\circ}$) being more laevorotatory than the α -D-manno-compound (I; R = H, X = OAc) ($[\text{M}]_{\text{D}} +78^{\circ}$). The application of the Conformational Dissymmetry Rule to these mercurials and also to the mercuriation products of D-galactal and its triacetate was studied to ascertain whether an explanation of the anomalous rotations could be found.

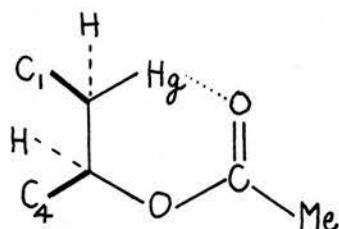
It was found that this method does not appear to be applicable to these sugar mercurials because agreement was not observed between the experimental rotations and the values calculated from the structures already established for the mercurials (Part I). Furthermore, agreement could not be obtained by assuming that the mercury group had the alternative configuration (i.e. cis methoxymercuration) and similar

calculations on the mercurials in the 1C-chair conformation met with no success.

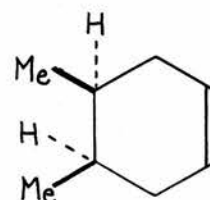
Since the anomalous rotations only appear in the acetylated mercurials, it was felt that these may be caused by a complexing between the carbonyl oxygen of the 3-acetoxyl group and the mercury atom to give cyclic complexes. Examination of models reveals that the relationship between the cyclic structures formed by complexing between the 3-acetoxyl group and the mercury atom would be enantiomeric in the β -D-gluc- and α -D-manno-mercurials. It would be predicted, therefore, that if the anomalous rotations found for the acetylated mercurials were caused by this cyclic complex formation, then the difference in the molecular rotations between the acetylated α -D-manno-mercurial and the corresponding deacetylated compound (i.e. $[M]_{OAc} - [M]_{OH}$) would be of the opposite sign to that observed for the β -D-gluc-mercurials. This prediction is in accordance with the experimental results, a value of $[M]_{OAc} - [M]_{OH} = -278^\circ$ being observed for the α -D-manno-mercurials as compared with the value of $+57^\circ$ for the β -D-gluc-isomers.

Brewster gives numerous examples of the large rotation changes which accompany cyclic complex formation and indicates a method of assessing the rotatory effects of ring formation. Thus, he is able to explain the rotations of α -amino and α -hydroxy acids by assuming the existence of a cyclic structure formed by hydrogen bonding between the carboxyl group and the α -substituent.^{1a} It was felt, therefore, that the similar cyclic

structure (Figure III, i) formed by complexing between the carbonyl oxygen of the 3-acetoxy group and the mercury atom in the α -D-manno-mercurial may be regarded, for conformational dissymmetry purposes, as equivalent to the disubstituted cyclohexene shown in Figure III, (ii).



(i)

Figure III

(ii)

Calculations showed that the cyclohexene derivative (Fig. III, ii) should have a small dextrorotatory rotation, which suggests that the conversion of the deacetylated mercurial (I; R = H, X = OAc) to the acetylated compound (I; R = Ac, X = Cl) should result in a small positive value being observed for $[M]_{\text{OAc}} - [M]_{\text{OH}}$. This prediction is contrary to the experimental results, a value of -278° being found for $[M]_{\text{OAc}} - [M]_{\text{OH}}$. A similar calculation on the cyclohexene derivative corresponding to the cyclic complex of the β -D-gluco-mercurial (II; R = Ac, X = Cl) suggests that the conversion of the deacetylated mercurial (II; R = H, X = OAc) to this acetylated product should result in a large negative value being observed for $[M]_{\text{OAc}} - [M]_{\text{OH}}$; the experimental value, however, was found to be $+57^\circ$. These

results underline the unreliability of the above comparison between the cyclic complexes postulated for the acetylated mercurials and the cyclohexene derivatives.

The infrared spectra of the acetylated mercurials were recorded on a Perkin-Elmer Model 237 Infracord Spectrophotometer and compared with the spectra of the corresponding glycoside tetraacetates to ascertain whether complexing between the carbonyl oxygen of the 3-acetoxyl group and the mercury could be demonstrated in the former compounds. Thus, it might be expected that the carbonyl group would have a larger contribution from the canonical form $\text{>}\overset{\delta+}{\text{C}}\text{---}\overset{\delta-}{\text{O}}$ in the complexed state, and this grouping would be expected to appear at lower frequency in the infrared. Although the spectra suggested the existence of a shoulder on the carbonyl peak of the mercurials, this result is unreliable since a similar shoulder was also observed with several of the glycoside tetraacetates.

Collins and Schwarz¹⁰¹ have recently recorded the optical rotatory dispersion curves of the mercurials from D-glucal, D-galactal and their triacetates in methanol. This work revealed that the rotations of the acetylated α -D-manno-mercurial (I; R = Ac, X = Cl) and the structurally similar α -D-talo-mercurial (IX; R = Ac, X = Cl) fell off rapidly at lower wavelengths, a negative extremum at 225 μ being observed for the latter compound. Since the rotation of the deacetylated α -D-talo-mercurial (IX; R = H, X = Cl) increased steeply in the lower wavelength region, this behaviour being in sharp contrast to

that of the triacetate above, it would be tempting to ascribe the low D-line rotations of the acetylated talo- and manno-mercurials to a negative Cotton effect due to acetoxyl. This explanation for the anomalous rotations of these acetylated mercurials would appear to be incorrect, however, because a negative extremum at 225 $m\mu$ was also observed for the acetylated β -D-gluco-mercurial (II; R = Ac, X = Cl), which is dextrorotatory at the D-line.

The Application of the Conformational Dissymmetry Rule to the Optical Rotations of Methylated Sugars and Related Compounds.

In calculating the optical rotations of free sugars and glycosides by the Conformational Dissymmetry Rule, Brewster^{1b} made use of six empirical parameters. Two of these parameters, $k(C - H)(O - H) = 50^\circ$ and $k(O - H)^2 = 45^\circ$, which have been shown to be widely applicable, are used to calculate the interactions between groups on adjacent ring carbon atoms; the remaining parameters are peculiar to pyranose sugars. Thus, two of the parameters are necessary to account for permolecular contributions to the rotation which arise from the existence of an axis of polarisability difference between $C_{(4)}$ and the oxygen of the pyranose ring, while the remaining two parameters reflect the sterically asymmetric environments of the methoxyl group in glycosides and the hydroxymethyl group in hexoses.

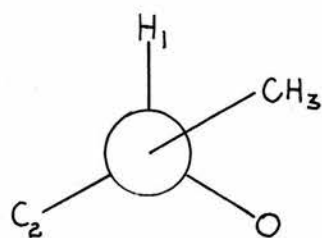
Although Brewster^{1b} had considerable success in calculating the rotations of a considerable number of sugars and glycosides using the above parameters, no attempt was made to extend this

method to methylated sugars. Since the relation between rotation and structure in the latter would be of interest as regards optical rotatory dispersion studies, the applicability or otherwise of the Conformational Dissymmetry Rule to these compounds was examined. Our approach to this problem was to apply the Conformational Dissymmetry Rule to a large number of fully methylated pyranoses of known rotations, denoting the various parameters involving methoxyl groups by symbols, and then to solve the series of simultaneous equations to obtain values for these parameters, analogous to those obtained by Brewster for hydroxyl.^{1b} It was found, however, that even the most satisfactory values for the parameters obtained by this treatment gave only a poor agreement between the calculated and experimental rotations. Examination of models indicates that the bulky methoxyl groups in these compounds, unlike the hydroxyl groups in free sugars, are unable to exist with equal probability in the three equilibrium positions about the bonds joining them to the ring, and thus the poor agreement between the observed and calculated rotations is hardly surprising.

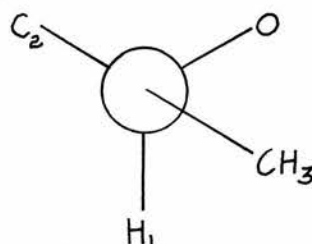
The set of parameters, which was obtained by a similar treatment to the glycoside tetraacetates, was found to give equally unpromising results.

It has been mentioned earlier that an extra parameter is required in the calculation of the rotations of methyl glycosides to reflect the sterically asymmetric environment of the methoxyl group which results from the loss of symmetry about

the bond joining this bulky group to the ring. Brewster^{1b} considers that α - and β -glycosides assume the conformations shown in (i) and (ii), Figure IV, and allows $+105^\circ$ and -105° respectively.

 α -glycoside

(i)

 β -glycoside

(ii)

Figure IV

It should be possible, by analogy with the above, to discover the most likely conformation which a methoxyl group will assume in other positions of the pyranose ring in methylated sugars, and thereby predict the molecular rotation change, $[M]_{\text{Me}} - H$, which will result on methylating that position. Examination of models indicates that the conformation which a methoxyl group will adopt will be determined by the stereochemistry of the groups (e.g. OH, OMe, CH_2OH or CH_2OMe) on adjacent ring carbon atoms. In Table II are presented the signs of the molecular rotation changes to be expected on the introduction of a methoxyl group into various environments on carbons 2, 3 and 4 of the pyranose ring in the C_1 -chair conformation; the terms $a_1a_2e_3$ etc. being used to describe the environment of the methoxyl group being considered. Thus, the term, $a_1e_2e_3 = +$,

indicates that a dextrorotatory molecular rotation change is to be expected on the introduction of an equatorial methoxyl group onto $C_{(2)}$, there being an axial group on $C_{(1)}$ and an equatorial group on $C_{(3)}$. Rotation changes of zero have been assumed for situations in which the methoxyl group can exist with equal probability in two similar conformations of opposite sign. Furthermore, the introduction of a methoxyl group onto the hydroxymethyl group of hexoses has been assumed to involve no rotation change.

Table II

Predicted Molecular Rotatory Contributions of Methoxyl Groups
in Various Environments of the Pyranose Ring.

OMe on $C_{(2)}$

A. $e_1 a_2 e_3 = 0$

C. $e_1 e_2 e_3 = 0$

B. $a_1 a_2 e_3 = -$

D. $a_1 e_2 e_3 = +$

OMe on $C_{(3)}$

E. $e_2 e_3 e_4 = 0$

G. $e_2 e_3 a_4 = +$

F. $a_2 e_3 e_4 = -$

OMe on $C_{(4)}$

H. $e_3 a_4 e_5 = 0$ (hexoses)
 $= +$ (pentoses)

I. $e_3 e_4 e_5 = 0$ (hexoses)
 $= -$ (pentoses)

These symbols, A, B etc., will be used to denote the various environments of the methoxyl groups shown in Table II. However, when the sugar derivative being examined exists in the $1C$ -chair conformation (e.g. derivatives of \underline{L} -fucose and \underline{L} -rhamnose),

these symbols will be followed by a dash, i.e. A', B' etc., and the predicted molecular rotatory contribution will have the sign opposite to that given in Table II for the corresponding environment in the C₁-chair conformation.

The predicted values for the sign of the molecular rotation change, $[\text{M}]_{\text{Me}-\text{H}}$, along with the observed values for the sign and magnitude of this change for a large number of methylated sugars and glycosides, are given in Table III.

Table III

Predicted and Observed Molecular Rotatory Contributions of Methoxyl Groups in Methylated Sugars and Glycosides.

Methylated Compound	Methoxide Environment	Predicted $[\text{M}]_{\text{Me}-\text{H}}$	Observed $[\text{M}]_{\text{Me}-\text{H}}$
Methyl 2-Me- β -D-galactoside	C	0	+4 ⁰
Methyl 3-Me- β -D-galactoside	G	+	+66
Methyl 2,4-Me ₂ - α -D-galactoside	D,H	+,0	-64
Methyl 2,4-Me ₂ - β -D-galactoside	C,H	0,0	0
Methyl 2,6-Me ₂ - β -D-galactoside	C	0	+4
Methyl 2,3,4-Me ₃ - α -D-galactoside	D,G,H	+,+,0	+88
Methyl 2,4,6-Me ₃ - α -D-galactoside	D,H	+,0	+7
Methyl Me ₄ - α -D-galactoside	D,G,H	+,+,0	+91
Methyl Me ₄ - β -D-galactoside	C,G,H	0,+,0	+49
2-Me- β -D-galactose	C	0	0
3-Me- α -D-galactose	G	+	+20
4-Me- β -D-galactose	H	0	+25
2,4-Me ₂ - α -D-galactose	D,H	+,0	-2

Table III (continued).

2,3-Me ₂ -β-D-galactose	C, G	0, +	+40°
2,6-Me ₂ -β-D-galactose	C	0	+5
3,4-Me ₂ -β-D-galactose	G, H	+, 0	+102
4,6-Me ₂ -α-D-galactose	H	0	+4
2,3,4-Me ₃ -α-D-galactose	D, G, H	+, +, 0	+60
2,4,6-Me ₃ -α-D-galactose	D, H	+, 0	+3
2,3,4,6-Me ₄ -α-D-galactose	D, G, H	+, +, 0	+110
2,3,4,6-Me ₄ -β-D-galactose	C, G, H	0, +, 0	+146
Methyl 2-Me-α-D-glucoside	D	+	+13
Methyl 2-Me-β-D-glucoside	C	0	-12
Methyl 3-Me-β-D-glucoside	E	0	+12
Methyl 2,3-Me ₂ -α-D-glucoside	D, E	+, 0	+24
Methyl 2,6-Me ₂ -α-D-glucoside	D	+	+37
Methyl 2,6-Me ₂ -β-D-glucoside	C	0	-30
Methyl 3,4-Me ₂ -β-D-glucoside	E, I	0, 0	+40
Methyl 2,3,6-Me ₃ -β-D-glucoside	C, E	0, 0	+4
Methyl 3,4,6-Me ₃ -β-D-glucoside	E, I	0, 0	+49
Methyl 2,4,6-Me ₃ -β-D-glucoside	C, I	0, 0	+6
Methyl Me ₄ -α-D-glucoside	D, E, I	+, 0, 0	+68
Methyl Me ₄ -β-D-glucoside	C, E, I	0, 0, 0	+23
2-Me-β-D-glucose	C	0	-11
3-Me-α-D-glucose	E	0	0
3-Me-β-D-glucose	E	0	+28
4,6-Me ₂ -α-D-glucose	I	0	+27

Table III (continued).

3,4,6-Me ₃ -α-D-glucose	E, I	0, 0	+2°
3,4,6-Me ₃ -β-D-glucose	E, I	0, 0	+57
2,3,4,6-Me ₄ -α-D-glucose	D, E, I	+, 0, 0	+15
Methyl 4-Me-α-D-mannoside	I	0	+20
Methyl 3,4-Me ₂ -α-D-mannoside	F, I	-, 0	-5
Methyl 4,6-Me ₂ -α-D-mannoside	I	0	+20
Methyl 2,3,4-Me ₃ -α-D-mannoside	B, F, I	-, -, 0	-43
Methyl Me ₄ -α-D-mannoside	B, F, I	-, -, 0	-47
Methyl Me ₄ -β-D-mannoside	A, F, I	0, -, 0	-66
4-Me-α-D-mannose	I	0	+10
2-Me-α-D-mannose	B	-	-39
3,4,6-Me ₃ -α-D-mannose	F, I	-, 0	-6
2,3,4,6-Me ₄ -α-D-mannose	B, F, I	-, -, 0	-26
Methyl 4-Me-β-D-xyloside	I	-	-15
Methyl 3,4-Me ₂ -β-D-xyloside	E, I	0, -	-26
Methyl 2,3,4-Me ₃ -α-D-xyloside	D, E, I	+, 0, -	-21
Methyl 2,3,4-Me ₃ -β-D-xyloside	C, E, I	0, 0, -	-60
3-Me-α-D-xylose	E	0	-50
2,3,4-Me ₃ -α-D-xylose	D, E, I	+, 0, -	-18
Methyl 4-Me-α-L-rhamnoside	I'	0	-16
Methyl 4-Me-β-L-rhamnoside	I'	0	-197
Methyl 2,3,Me ₂ -α-L-rhamnoside	B', F'	+, +	+100
Methyl 2,3,4-Me ₃ -α-L-rhamnoside	B', F', I'	+, +, 0	+79
Methyl 2,3,4-Me ₃ -β-L-rhamnoside	A', F', I'	0, +, 0	+63

Table III (continued).

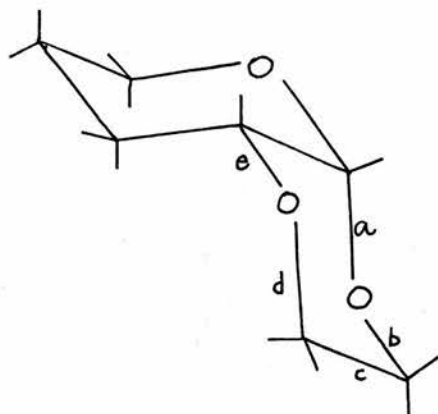
Methyl 3-Me- α - <u>L</u> -fucoside	G'	-	-18°
Methyl 2,3-Me ₂ - α - <u>L</u> -fucoside	D', G'	-, -	-42
Methyl 3,4-Me ₂ - α - <u>L</u> -fucoside	G', H'	-, 0	-90
Methyl 2,3,4-Me ₃ - α - <u>L</u> -fucoside	D', G', H'	-, -, 0	-110
Methyl 2,3,4-Me ₃ - β - <u>L</u> -fucoside	C', G', H'	0, -, 0	-73
Methyl 2,3,4-Me ₃ - α - <u>L</u> -arabinoside	C, G, H	0, +, +	+67
Methyl 2,3,4-Me ₃ - β - <u>L</u> -arabinoside	D, G, H	+, +, +	+112

The optical rotations of the free sugars and glycosides, and of their methylated derivatives, from which the values of $[M]_{Me-H}$ in Table III were obtained, were recorded in water and taken from various sources.¹⁰²

The results given in Table III indicate that our relationship has only been moderately successful in predicting the molecular rotation change on methylation, 48 correct predictions being made in the 68 methylated compounds examined. When it is considered, however, that each molecular rotation change, $[M]_{Me-H}$, can have a zero, negative or a positive value, the degree of success found is quite encouraging. Although the results would appear to confirm the essential correctness of our postulate that the conformation adopted by a methoxyl group is important in determining the change in rotation on methylation, there are undoubtedly other factors involved which were not considered in this preliminary treatment.

The above treatment was extended to predicting the molecular rotation change which would accompany 1,2-O-ethylene ring formation; the conformations of these fused ring compounds are fixed by the rigidity of the system and thus it was felt that it might also be possible to predict the approximate magnitude of this rotation change.

The experimental values, $[M]_{\text{expt.}}$, Table IV, which denote the observed molecular rotation change accompanying ring formation, were the difference in the molecular rotations of the 1,2-O-ethylenepyranose¹⁰³ and the corresponding glycoside.¹⁰⁴ The glycoside, and not the free sugar, was chosen for comparison purposes because the rotation of the former can be obtained with greater accuracy. The predicted molecular rotation changes, $[M]_{\text{calc.}}$, Table IV, which accompany the formation of 1,2-ethylene- α - and β -pyranoses, were obtained by a summation of the various contributions to the molecular rotation of the individual bonds in the dioxan ring. Since the rotation of the methyl glycoside was taken for comparison purposes, it is necessary to add a value of -105° to the predicted rotation of the 1,2-O-ethylene- α -pyranose, and a value of $+105^\circ$ to that of the β -pyranose, to account for the change in the environment of the glycoside group which results on ring formation.^{1b} The calculation of the molecular rotation change to be expected on the formation of a 1,2-O-ethylene- α -D-pyranose is shown on the following page.

1,2-O-ethylene-α-D-pyranose

<u>Bond</u>	<u>Predicted Rotatory Contribution</u>
a	$-kC(C - H)$
b	$+kC(C - H)$
c	$-k(O - H)^2$
d	$+kC(C - H)$
e	0
	<u>-105</u>

$$\begin{aligned}
 \therefore [M]_{\text{calc.}} &= kC(C - H) - k(O - H)^2 - 105^\circ \\
 &= 110 - 45 - 105^\circ \\
 &= \underline{-40^\circ}
 \end{aligned}$$

A value of 110° was taken for the term $kC(C - H)$ by comparison with the value of 105° assigned by Brewster^{1b} to the similar product $kC(O - H)$.

A similar treatment to the above on the β -isomer gives:

$$\begin{aligned}
 [M]_{\text{calc.}} &= +k(O - H)^2 + 105^\circ \\
 &= \underline{+150^\circ}
 \end{aligned}$$

The observed and calculated values for the molecular rotation change accompanying the formation of a 1,2-O-ethylene ring on a variety of sugars are shown in Table IV. The rotations of the 1,2-O-ethylene-D-pyranoses,¹⁰³ and the corresponding glycosides,¹⁰⁴ from which the values of $[M]_{\text{expt.}}$ were derived, were all recorded in water.

Table IV

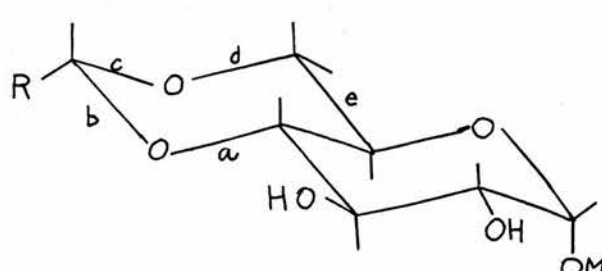
Predicted and Observed Molecular Rotation Changes accompanying
1,2-O-Ethylene Ring Formation.

<u>1,2-O-Ethylenepyranose.</u>	$[M]_{\text{calc.}}$	$[M]_{\text{expt.}}$
1,2-O-ethylene- α -D-glucose	-40°	-110°
1,2-O-ethylene- β -D-glucose	+150	+180
1,2-O-ethylene- β -D-galactose	+150	+172
1,2-O-ethylene- β -D-maltose	+150	+165
1,2-O-ethylene- β -D-cellobiose	+150	+190
1,2-O-ethylene- β -D-lactose	+150	+170

The observed values for the molecular rotation changes accompanying the formation of 1,2-O-ethylene- β -pyranoses appear to be almost identical for the sugars examined. This result is in agreement with our postulate that the rotation change on ring formation will be determined by the interactions along each bond of the dioxan ring and should therefore be almost independent of the sugar residue. Although a close agreement has been obtained between the calculated and observed values for the rotation change accompanying the formation of 1,2-O-ethylene- β -pyranoses, the large discrepancy in these values for the α -isomer is disturbing. Consideration of Brewster's work on the pyranose sugars suggests that the presence of the 1,2-ethylene ring lying below the pyranose ring in 1,2-O-ethylene- α -pyranose should make a permolecular contribution to the molecular rotation, which would be absent in the flatter molecule

of the β -isomer. Although this permolecular effect may be the cause of the discrepancy in the rotations found for the 1,2-O-ethylene- α -pyranose, this would appear unlikely because a small dextrorotatory permolecular effect would be expected from a consideration of the Conformational Dissymmetry Rule (see Ref. 1b) and not a laevorotatory contribution as suggested from the results given in Table IV.

The application of this treatment to predicting the sign, and perhaps the magnitude, of the molecular rotation change accompanying 4,6-ethylidene or benzylidene ring formation was studied. The method of calculating the rotation change was essentially that given above for 1,2-O-ethylenepyranses involving a summation of the rotatory contributions of the interactions along the bonds of the alkylidene ring. It was necessary, however, to subtract a value of $+25^\circ$ from the rotation thus calculated to allow for the change in the environment of the sterically asymmetric hydroxymethyl group (see Ref. 1b). The calculation of the molecular rotation change, $[M]_{\text{calc.}}$, Table V, to be expected on the formation of 4,6-alkylidene-D-glucopyranoside is shown below:

	<u>Bond</u>	<u>Predicted Rotatory Contribution</u>
	a	$-kC(C - H)$
	b	$+kC(O - H)$
	c	$-kC(O - H)$
	d	$+kC(C - H)$
	e	$-k(C - H)(O - H)$
4,6-alkylidene- <u>D</u> -glucopyranoside		<u>-25</u>

$$\begin{aligned}\therefore [M]_{\text{calc.}} &= -k(C - H)(O - H) - 25^\circ \\ &= \underline{-75^\circ}\end{aligned}$$

A similar treatment to the above on 4,6-alkylidene-D-galactopyranoside gives:

$$\begin{aligned}[M]_{\text{calc.}} &= k(C - O)(O - H) - 25^\circ \\ &= \underline{-20^\circ}\end{aligned}$$

Brewster^{1b} assigns a value of $+5^\circ$ to the term $k(C - O)(O - H)$.

The observed rotation changes, $[M]_{\text{expt.}}$, which were the difference between the molecular rotations of the alkylidene glycoside¹⁰⁵ and the corresponding free glycoside¹⁰⁴ (all rotations being recorded in water), are shown in Table V along with the predicted values, $[M]_{\text{calc.}}$.

Table V

Predicted and Observed Molecular Rotation Changes accompanying 4,6-Ethylidene and Benzylidene Ring Formation.

<u>4,6-Alkylidene Compound.</u>	$[M]_{\text{calc.}}$	$[M]_{\text{expt.}}$
Methyl 4,6-ethylidene- α -D-glucoside	-75°	-69°
Methyl 4,6-benzylidene- α -D-glucoside	-75	-59
Methyl 4,6-ethylidene- β -D-glucoside	-75	-108
Methyl 4,6-benzylidene- β -D-glucoside	-75	-154
Methyl 4,6-benzylidene- α -D-mannoside	-75	-83
4,6-Ethylidene- α -D-galactose	-20	-26^*
Methyl 4,6-benzylidene- β -D-galactoside	-20	-15

* Note: this value is the difference in the molecular rotations of the ethylidene-D-pyranose and α -D-galactopyranose.

The results given in Table V indicate that a fair agreement has been obtained between the observed and calculated values for the molecular rotation change accompanying 4,6-alkylidene ring formation, except for the derivatives of methyl β -D-glucoside. The discrepancy found for the latter compounds is surprising since a permolecular contribution to the optical rotation would appear to be unlikely in these compounds.

The investigation into the application of the Conformational Dissymmetry Rule to the rotations of a variety of sugar derivatives, which has been discussed in this section, illustrates the limitations of this Rule when applied to more complicated structures. Unknown permolecular and other effects, such as solvation, undoubtedly bedevil some of the calculations and probably account for some of the discrepancies found in predicting sign and magnitude of rotation changes.

Preliminary Experiments on the Application of Circular Dichroism and Optical Rotatory Dispersion in Carbohydrate Chemistry.

A beam of plane polarised light may be considered to be made up of a left and a right circularly polarised component. These components will travel with different velocities in a medium which has different refractive indices for left and right circularly polarised light (i.e. a "circularly birefringent medium"), with the result that the plane of polarisation is rotated. If the medium also has different absorption coefficients for these circularly polarised components, then the resulting light will be elliptically polarised and the medium

is said to exhibit "circular dichroism".

Although optical rotatory dispersion has now come to be a valuable structural tool, largely due to the pioneering work by Djerassi and his school, little work has been done on the correlation of circular dichroism to molecular structure. This is largely due to the difficulty which has previously been experienced in the measurement of circular dichroism in the ultraviolet. However, the recent development of a commercial instrument for the rapid measurement of circular dichroism (the Roussel-Jouan Dichrograph), now provides chemists with an additional physical means of investigating molecular structure and stereochemistry. Since the circular dichroism associated with an absorption band is confined to the region of absorption, circular dichroism spectra should in general be easier to interpret than rotatory dispersion curves, since the latter are the sum of the partial rotations of a number of asymmetric chromophores.

In order to assess the usefulness of circular dichroism in carbohydrate chemistry, arrangements were made with the manufacturers of the Roussel-Jouan Dichrograph to examine a number of typical carbohydrate derivatives. Since this instrument measures directly the difference in the molar extinctions of left and right circularly polarised light ($\Delta\epsilon = \epsilon_L - \epsilon_R$), it was hoped to detect the dichroism of strongly absorbing groups (i.e. large ϵ) of weak anisotropy (i.e. small $\Delta\epsilon/\epsilon$). With this view, the spectra of methyl 2-O-tosyl- α -D-glucopyranoside

and 1-O-benzoyl- β -D-glucose tetraacetate were recorded. Although the former compound gave unpromising results, any dichroism present being swamped by the strongly absorbing tosyl group, the spectrum of the latter compound was very interesting. Thus, the spectrum of the benzoate in ethanol showed a weak negative dichroism of $\Delta\epsilon$ ca. -0.1 at λ_{max} . 280 $m\mu$ followed by a strong positive dichroism at lower wavelength, e.g. $\Delta\epsilon$ ca. +1 at λ 246 $m\mu$ (maximum not reached because of the high absorption of the benzoate group). Since only the benzoate group is absorbing in this region of the spectrum, this indicates that the observed negative and positive Cotton effects arise from two different transitions involving this group.

The optical rotatory dispersion of this benzoate in methanol, which was kindly determined by Professor W. Klyne and Mr. J. Jennings of the University of London, gave unpromising results, a plain negative curve being obtained (RD in methanol; $[M]_{500}$ -40° ; $[M]_{300}$ -150° ; $[M]_{246}$ $-1,220^\circ$). This preliminary result would suggest that for systems which absorb in the near ultraviolet, circular dichroism might give more information about structural changes than optical rotatory dispersion.

Methyl α -D-glucopyranoside tetraacetate has been found to give abnormally high rotations in certain benzenoid solvents which have been attributed by Riddick and Schwarz¹⁰⁶ to solvent-solute interactions, which probably involve charge transfer processes. The circular dichroism spectrum of this compound in benzene was examined in the hope that it might show

measurable dichroism in the region of the benzene absorption bands which would be caused by asymmetric interactions between the tetraacetate and the solvent. It was found, however, that although the spectrum of this solution suggested the existence of dichroism in this region, the absorption of the solvent was too great for this to be stated with certainty.

Circular dichroism and optical rotatory dispersion of methyl α -D-glucopyranoside tetraacetate were recorded to ascertain whether the acetoxyl group would show observable Cotton effects.

The circular dichroism spectrum of the tetraacetate in ethanol revealed a negative dichroism with $\Delta\epsilon$ ca. -3.0 at 210 $m\mu$ (the maximum of this dichroism, which was outside the range of this instrument, is probably at 208 $m\mu$ to coincide with the maximum observed in the ultraviolet spectrum of this compound). The negative Cotton effect observed must be caused by an acetoxyl group and further work on mono and diacetates is clearly desirable to ascertain the group(s) responsible. It is unfortunate that the application of the Conformational Dissymmetry Rule to acetylated glycosides was unsuccessful, because this might have provided a simple means of ascertaining the acetate group which causes the negative Cotton effect.

The optical rotatory dispersion of methyl α -D-glucopyranoside tetraacetate showed a plain positive curve with a suggestion of a shoulder at λ 241 $m\mu$ which may be caused by the negative Cotton effect due to acetoxyl being superimposed on

the large positive absorption of the glycoside group (RD in methanol, c 0.4792; $[M]_{589} +487^\circ$; $[M]_{500} +551^\circ$; $[M]_{400} +1,160^\circ$; $[M]_{300} +2,380^\circ$; $[M]_{250} +3,744^\circ$; $[M]_{241} +3,890^\circ$, shoulder; $[M]_{222} +5,560^\circ$; $[M]_{208} +11,470^\circ$). It is of interest to note that the plot of the Faraday current against wavelength showed a distinct negative extremum in this region.

This preliminary investigation suggests that circular dichroism will be more useful and probably easier to interpret than the closely related phenomenon of optical rotatory dispersion.

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